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SOME ASPECTS OF HAEMOGLOBIN BIOSYNTHESIS AND THEIR IMPORTANCE TO MEDICINE*

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Until recently our knowledge of the synthesis of haemoglobin in the body was so scanty that it could be summarized in a few lines. The site of haemoglobin formation in the adult was known to be the red bone-marrow, and haemoglobin could be observed to occur at a certain stage in the development of the cell destined ultimately to become a circulating erythrocyte. In foetal life, or under great stress, other organs, such as the liver, were capable of showing haemopoietic activity. Certain perturbations of haemoglobin biosynthesis were also known and understood to a greater or lesser degree. Thus, simple iron deficiency resulted in an anaemia of microcytic type with poor haemoglobinization of the cell, understandably due to inability to synthesize adequate amounts of haem, the iron-containing pigmented moiety of haemoglobin. In some other forms of anaemia the mechanism was—and to this day still is—little understood. I refer to such states as the anaemias accompanying chronic infections, malignant disease, and so on.

Experimental Work

The first great contribution to the biochemistry of haemoglobin biosynthesis was made by Whipple and his associates, who used dogs kept anaemic by repeated withdrawals of blood and return of the plasma after centrifugation. If animals were required to be both anaemic and deficient in plasma proteins, no restoration was made, and, similarly, by returning the cellular elements but no plasma, a state of plasma-protein deficiency without anaemia could be produced. The basal diet was a poor one—bread and fish-paste—and supplementary proteins or amino-acids could be added at will. Whipple's experiments demonstrated that such dogs had a high power of haemoglobin restoration even when completely starving, that biosynthesis of haemoglobin took precedence over that of plasma proteins, and that different dietary proteins added to the basal diet showed differing degrees of biological efficiency calculated from the number of grammes of haemoglobin synthesized per 100 g. of such protein fed.

It is perhaps not surprising that the protein most efficiently utilized was haemoglobin itself, followed closely by such relatively complete proteins as casein, plasma protein, and liver. The vegetable proteins, so often deficient in one or more essential amino-acids, had a relatively low biological value. Only the globin moiety and not the haem of administered haemoglobin was used for erythropoiesis, since after intraperitoneal injection of haemoglobin into the anaemic animal its constituent haem was promptly excreted as extra bile pigment while the globin was utilized with 80–90% efficiency.

That the biological value of a protein for haemoglobin synthesis depends upon its amino-acid composition is substantiated by feeding protein hydrolysates or pure amino-acid mixtures and also by experiments in which haemoglobin synthesis is followed by incubating reticulocytes with an appropriate mixture of amino-acids. In the whole animal with exhausted body protein stores, it is the amino-acid in shortest supply in the supplement, as compared with its quantity in the haemoglobin molecule, which will become the limiting factor and determine how much haemoglobin can be produced. Thus Sebrell (1949) found that in rats the most effective supplement for haemoglobin regeneration was histidine, with valine, lysine, phenylalanine, and leucine following closely in that order. No dietary amino-acid plays a convincingly "specific" part.

The work of Aschkenasy and Pariente (1951) on the protective effect of methionine against protein-deficiency anaemia is explicable, it would seem, on the basis of the participation of methionine, together with vitamin B_{12} and folic acid, in the metabolism of one-carbon fragments required in the biosynthesis of nucleoproteins. The conversion of tryptophan into nicotinic acid is controlled by pyridoxine, and deficiency of any one of these three factors will cause anaemia, but the supplementation of a niacin-deficient diet with tryptophan is protective. A finding rather more difficult to understand is the report by Orten, Bourque, and Orten (1945) that when rats are fed upon beef globin as the sole source of protein the addition of isoleucine promotes haemoglobin formation. This is strange, since the haemoglobins so far analysed are free from isoleucine. The haemoglobin of the rat may be an exception, but it appears more likely that this is a sparing action, the inclusion of isoleucine in the diet reducing breakdown of body proteins and hence rendering available more dietary protein for the synthesis of haemoglobin.

Normal Haemoglobin Synthesis

To return to our consideration of the source of material for haemoglobin synthesis in the normal organism, there are clearly three possible sources of protein or protein-breakdown products which could be drawn upon—namely, (1) dietary protein ; (2) protein stores in organs, tissues, and

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plasma; and (3) the protein, mainly globin, liberated through the continuous normal destruction of red cells—and I shall deal with each of these possibilities in turn. The description which I have already given of Whipple's work and experiments by other investigators makes it quite clear that good dietary protein may provide all that is required for the biosynthesis of haemoglobin, assuming, of course, that iron, vitamins, and so forth are in sufficient supply.

During starvation, body protein is broken down to counteract anaemia caused by deliberate withdrawal of red cells. In the normal well-fed animal we may expect the pool of free amino-acids in the tissues to be drawn upon for haemoglobin restoration, and there are also protein stores present, particularly in the liver. This was clearly recognized by Whipple as a result of his experiments. All these sources can be drawn upon freely and indiscriminately for haemoglobin biosynthesis; we have no convincing evidence for the existence of specific erythropoietic stores.

Utilization of Red-cell Catabolites

Finally, let us consider the possibility of a preferential utilization of red-cell catabolites. It is possible that the proteins of destroyed erythrocytes could be directly and specifically re-utilized for red-cell regeneration. It is even conceivable that such a mechanism could be responsible, in part at least, for the remarkably constant equilibrium that is maintained between regeneration and destruction of red cells. We know for a fact that iron is used again in haemoglobin biosynthesis.

Various types of experiment have been devised in attempts to answer this question. Increased haemolysis provoked by agents such as phenylhydrazine is followed immediately by enhanced haemoglobin synthesis, which might suggest re-utilization of globin after more or less complete degradation, but a more decisive experiment, affording no support for such re-utilization, was performed by Bale, Yuile, DeLaVergne, Miller, and Whipple (1949). They fed the amino-acid lysine, labelled by ^{14}C in its ε position, to a dog depleted of both haemoglobin and plasma proteins. The animal was thereafter given a good diet, and determinations of ^{14}C in the washed cells and plasma respectively were made at intervals for the next 234 days. Haemoglobin was not actually separated for determination of radioactivity, but in a parallel experiment on a rat it was shown that the ^{14}C of lysine, when administered under similar conditions, was confined almost exclusively to globin within the red cell. Haemoglobin makes up about 90% of the solid matter of the erythrocyte, so that the intensity of labelling of the whole cell could be taken to indicate that of globin, *provided there is no other very metabolically active protein present.*

The experimental results showed a rapid labelling of plasma protein, which fell again, roughly exponentially, at a rate indicating a turnover time of about 10 days. Red-cell protein reached its maximum radioactivity rather more slowly, after which the curve exhibited a plateau followed by a fairly sharp fall from the 80th to 150th day. The similarity of this picture to that of haem labelling after the feeding of ^{15}N glycine (Shemin and Rittenberg, 1946) is striking, and the same conclusions are permissible—namely, that the protein fraction investigated (assumed to be globin) is outside the general dynamic exchange of body protein constituents, has an average life of about 115 days, and is *not* preferentially re-utilized for the formation of new erythrocytes.

Order of Synthesis

If we accept that both the globin and haem moieties of haemoglobin are built up *de novo* in the biosynthesis of the pigment in the bone-marrow, we must now inquire whether these processes are simultaneous or whether, for example, globin is synthesized first and haem added later.

The molecule of haemoglobin consists of several layers of coiled polypeptide chains, and *x*-ray crystallographic measurements show that the four haem residues probably lie upon the surface of this structure. Prior synthesis of globin would not therefore be an unreasonable supposition. Experiments performed by Thorell (1947) seemed, in fact, to indicate that such was the case. Using a highly sensitive microspectrographic technique, he was able to measure in individual cells, aspirated from the bone-marrow, the content of nucleic acid, total protein, and haem. The absolute amounts of these substances were plotted against the stage of maturation, and curves were obtained which showed clearly that the synthesis of the total protein is largely completed before that of haem takes place, and *if* we assume this new protein to be mainly globin, then globin would appear to be synthesized first and haem added to it later on.

There is another way by which this point may be tested. It is known that eight molecules of glycine are utilized in the synthesis of one molecule of haem, and glycine is also required, of course, for incorporation into globin. By giving an animal 2-^{14}C labelled glycine, any pool of this amino-acid in the erythropoietic tissues should be uniformly labelled within a short time, and were new molecules of globin and of haem to be synthesized *simultaneously* from this pool one would expect to find a constant ratio of eight between the radioactivity of one mol of haem and that of one mol of glycine isolated from the globin portion of the same sample of haemoglobin. Ratios greater or less than eight would indicate prior synthesis of haem or of globin respectively. In such an experiment carried out on rabbits by Muir, Neuberger, and Perrone (1952), the figures obtained 24 hours and more after the administration of the radioactive glycine were consistent with simultaneous synthesis of globin and haem. At earlier intervals a lower ratio suggested some priority in globin synthesis, but the interpretation demands caution.

Yet another way of approaching this problem is by following the biosynthesis of haemoglobin by reticulocytes under suitable conditions *in vitro*. Kruh and Borsook (1956), and more particularly Nizet (1953, 1955, 1957), have used this method. In Nizet's scrupulously careful work, reticulocyte-rich dog blood is first incubated with the marker. The haem and globin fractions are then carefully purified, glycine is isolated as the pure dinitrophenyl derivative after hydrolysis of the globin, and the radioactivity of the two fractions is determined in the form of barium carbonate. His results point to a simultaneous synthesis of globin and of haem. Even more interesting is the fact that if he adds to the system agents which stimulate or depress *either* globin or haem formation, the other component rises

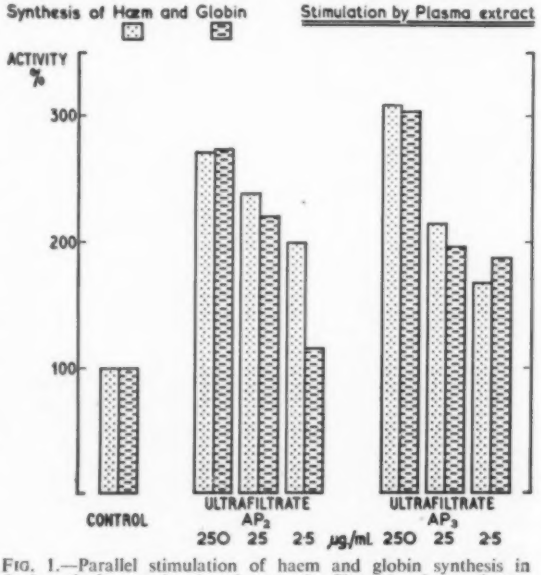

FIG. 1.—Parallel stimulation of haem and globin synthesis in dog's reticulocytes *in vitro* by an ultrafilterable plasma factor.

or falls in a parallel manner. We know that violent treatment such as haemolysis will destroy protein-synthesizing ability whilst leaving that of haem intact ; but in the complete normal cell Nizet concludes that the synthesis of haem regulates and controls that of globin. The parallelism is well exemplified in a series of unpublished experiments he and I performed together and in which we added a stimulating factor derived from plasma. This material considerably enhances haem production by red-cell haemolysates, but when added to the surviving reticulocyte preparation both globin and haem production are stimulated, and each to an approximately equal extent (Fig. 1).

Relation of Globin and Haem Synthesis

The mechanism by which globin synthesis is so precisely related to that of haem is at present obscure. The implications of this finding for the pathologist are, however, obvious. Although disability to synthesize haem is infrequent we have one clear example in iron-deficiency anaemia, and another perhaps in copper-deficiency anaemia, and the first authentic case in man of anaemia due to deficiency of pyridoxine in the diet has been recently described. Pyridoxine is known to be concerned in the elaboration of porphyrins and haem, and, according to the work of Dr. Goldberg, in Glasgow, so also is ascorbic acid, which apparently plays an important part in the final incorporation of the iron atom into protoporphyrin. The clinical association of some anaemias with ascorbic acid deficiency is well known.

I may pause here to recall an interesting finding of the Whipple school. It is that in a well-nourished dog the production of a sterile inflammatory lesion causes anaemia, lowering of plasma iron, and marked delay in the uptake of ^{59}Fe. A similar lesion in an already anaemic and iron-deficient dog does not, however, have these effects. It was concluded that anaemia following inflammation is relatively mild and easily overcome if the bone-marrow is already sufficiently stimulated. My own impression is that we have much more to learn about the interplay of the various factors stimulating or inhibiting biosynthesis of the two fragments of haemoglobin in pathological conditions such as this.

I purposely propose to avoid any review of the so-called haemopoietins. Enough has been said to indicate that plasma factors, at least, do exist but that more work has to be done upon isolated systems before the physiological tangle caused by crude stimulation, as by reduced oxygen tension, can be unravelled. Just how complex the situation may be is revealed by the demonstration given by Jacobson and co-workers (1957) of the essential part played by the kidney in response to such stimuli. It must either activate a precursor of a haemopoietin or elaborate and secrete such a precursor, which is then transformed into the physiologically active material at another site—a story reminiscent of hypertensin production from hypertensinogen under the influence of renin.

Gene-controlled Defects in Globin Production

An absolute inability to biosynthesize the globin moiety of haemoglobin would of course prove fatal, but there are certain examples of gene-controlled defects or abnormalities in globin production. The best known of these is sickle-cell anaemia, or trait, in which a certain proportion of the haemoglobin produced differs in its protein part from normal haemoglobin. Skilled biochemical work over the past few years has culminated in the discovery that the difference here lies in the substitution of a molecule of valine for a molecule of glutamic acid in one of the polypeptide chains or of globin (Ingram, 1956). Such a relatively slight abnormality has nevertheless serious consequences. As is well known, the reduced form of sickle-cell haemoglobin is so sparingly soluble that it can separate out in liquid crystal form in the affected erythrocyte.

Other gene-controlled abnormalities of globin synthesis leading to the appearance of haemoglobins differing from haemoglobin A in their electrophoretic mobility are encountered, and at least nine non-sickling haemoglobin variants are known. In haemoglobin C, lysine appears instead of glutamic acid in the same position in the peptide chain as was incriminated in the case of sickle-cell haemoglobin, but one of the most interesting of these abnormal haemoglobins is haemoglobin M, so named because it occurred as methaemoglobin in the red cells of a family with an unusual form of familial methaemoglobinaemia discovered by Hörlein and Weber in 1948. The defect is usually due to lack of a flavoprotein co-factor forming a link in the oxidation-reduction chain which keeps the haemoprotein in the erythrocyte in the ferrous form. In this family, however, the abnormality was in the structure of the globin itself, for, when this was exchanged for normal globin, reduction to ferrous haemoglobin offered no difficulty.

In Cooley's anaemia, Mediterranean anaemia, or thalassaemia, as it has been variously called, there is a genetic abnormality which shows itself in an inability to synthesize ordinary haemoglobin A. The homozygous condition results, therefore, in a severe and often fatal anaemia, whilst the heterozygous condition, thalassaemia minor, may also result in severe disability.

Biochemistry of Porphyrin Synthesis

Do genetically determined errors occur also in the biosynthesis of the porphyrins or haem part of haemoglobin ? The answer is, " Yes, so far as we know, in *one* instance ; in congenital porphyria." Drug-induced methaemoglobinaemia and sulphaemoglobinaemia arise through alterations of normal pigment, and I do not include them, therefore, under this heading.

In congenital porphyria, however, many immature and circulating red cells are loaded with porphyrins belonging to the abnormal isomeric series I. The haem isolated from the haemoglobin of these cells is the normal series III pigment ; the reason why none of the series I type haem is found is because there is an absolute specificity in the oxidative decarboxylation of coproporphyrin III to the corresponding protoporphyrin. This enzyme system is unable to utilize coproporphyrin I added to it in *in vitro* experiments, so we

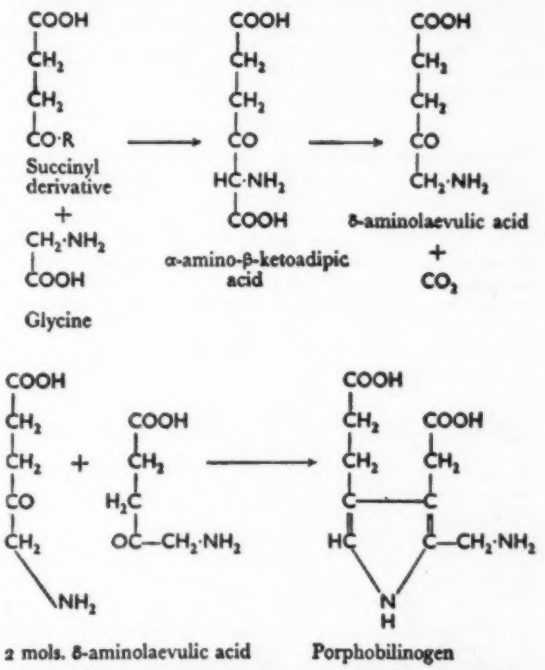

FIG. 2.—Scheme summarizing biosynthetic steps from glycine + succinate (from the tricarboxylic acid cycle) to porphobilinogen, the simplest pyrrolic substance known to be a precursor of haem and porphyrins.

have the picture of normal haem—that is, iron protoporphyrin—together with masses of uroporphyrin I and coproporphyrin I, the end stages of the abnormal synthesis proceeding in some erythrocytes.

To understand this situation in more detail it is necessary to recall what is now known about the biochemistry of porphyrin synthesis, and this I have summarized in Fig. 2. Glycine and succinic acid are the two simple materials from which the complex ring structure of porphyrin is built up. An initial condensation, for which pyridoxine and coenzyme A appear to be essential, results in the formation of δ-aminolaevulic acid. Two molecules of this substance are then combined in such a way that a pyrrolic substance is formed. This is porphobilinogen, the urinary excretion of large quantities of which, it is interesting to note, is the biochemical abnormality characterizing acute intermittent porphyria, a disease involving the liver rather than the haemopoietic system. Porphobilinogen can be transformed either chemically or enzymatically into uroporphyrin, and in each case it is the unsymmetrical series III isomer which is the principal product.

Many schemes have been put forward to explain the way in which combination of four identical porphobilinogen units could result in a porphyrin of this configuration, and I shall not discuss the merits and demerits of each hypothesis here. It is sufficient to note that this is the normal course of events. We (Booij and Rimington, 1957) have found, however, that if our enzyme system, extracted from red blood cells, is heated for some time at about 60° its character is altered so that when incubated with porphobilinogen it now forms exclusively uroporphyrin I, the symmetrical uroporphyrin isomer, which, as I have already said, is excreted in large quantities by congenital porphyrinurics. Not only this, but if we prepare an enzyme system from the erythrocytes of animals or human patients with congenital porphyria and incubate it with porphobilinogen *in vitro*, we find that both uroporphyrins I and III are formed and the series I isomer may even predominate (Rimington and Booij, 1957).

It is thus clear that by mild heat treatment of the enzyme system from normal cells we have made it resemble that of the congenitally abnormal cells of this rare familial disease. Just what happens as a result of heating is under investigation at the present moment in my department. When we know, we shall, I feel convinced, understand also the inborn error responsible for congenital porphyria.

Conclusion

In this survey I have tried to view haemoglobin biosynthesis as a whole and then to indicate how experimental findings over a wide field are slowly but steadily being related to various steps in this vital process. Nearly 100 years have elapsed since Körber (1866) first noticed the difference between foetal and adult haemoglobins, and we cannot flatter ourselves on the speed of our progress; nevertheless the record of the past few years holds out some promise that before another century dawns we may have achieved understanding and control of some, at least, of the medical problems associated with haemoglobin biosynthesis.

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THE PRODUCTION RATE OF CORTISOL IN MAN

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Hitherto the great majority of proposed measures of adrenal cortical activity have involved the estimation of a particular chemical group of metabolites in the urine. These have all suffered from the disadvantage that it has not been possible to check their validity by comparison with any more direct measure of adrenal activity, and the relation between the amount of excreted compounds and the actual production rate by the adrenal cortex has been a matter of considerable conjecture. Indeed, some tests have relied for their justification on little more than the observation that they give low readings in clinical hypoadrenalism and high readings in Cushing's syndrome.

One of the major products of the adrenal cortex is now proved to be cortisol (hydrocortisone), and measurement of the production rate of this hormone must therefore be regarded as one of the major indices of adrenal activity.

The recent introduction of radioactive cortisol, labelled with ^{14}C in ring A, has made possible a much more direct estimation of the rate of production of endogenous cortisol than could be achieved before. Peterson and Wyngaarden (1956) have pioneered its use for this purpose. By injecting trace amounts of ^{14}C-labelled cortisol into human subjects and by making serial estimations of the changing ^{14}C content (specific activity—S.A.) of the circulating cortisol they were able to calculate turnover rates by methods conventional in such isotope studies. In nine normal subjects they reported a mean daily cortisol production of 21 mg.

The estimates of these authors were based on events occurring during an observation period of two to four hours, and daily output was calculated on the assumption that the observed production rate persisted throughout the 24 hours, an assumption which is probably not justified. While such an estimate of production over a short period is valuable for many purposes, a simpler method capable of indicating the daily output without recourse to difficult serial analyses would also be of very great clinical value.

We suggest here an alternative method of using ^{14}C-labelled cortisol which is believed to give a useful estimate of the daily production of cortisol by the subject, which is relatively easy to apply clinically even to ill patients, and which does not make excessive demands on the time and skill of laboratory staff. Results in a variety of clinical conditions using this method are presented.

Principle

The principle of the measurement is the well-established one of isotope dilution. If a small amount of ^{14}C-labelled cortisol is introduced into the body it may be expected to be metabolized in precisely the same manner as the endogenous cortisol. It will thus enter equally into all the metabolites, known and unknown, of cortisol and will appear in these in the urine.

The radioactive cortisol will be diluted by the endogenous non-radioactive cortisol, and likewise all the metabolites will be diluted by the corresponding non-radioactive products of endogenous cortisol breakdown. The extent of this dilution can be found by determining the ^{14}C content (S.A.) of a representative excreted metabolite and comparing this with the ^{14}C content (S.A.) of the radioactive steroid administered. The ratio between the two specific activities indicates the degree of dilution, and if the mass of the radioactive cortisol dose be known the weight of endogenous cortisol and its metabolites necessary to effect this dilution can be simply calculated, being the dose times the dilution.

The method thus involves the separation of a suitable cortisol metabolite from the urine. Cortisol itself is present in urine but is not well suited for such an analysis because it is present only in low concentration averaging less than 50 μg. a day in normal urines (Cope and Hurlock, 1953).

Two major breakdown products of cortisol metabolism, tetrahydrocortisol and tetrahydrocortisone, are, however, present in urine in relatively large amounts, averaging together more than 2.5 mg. in normal urines. These tetrahydro compounds are excreted mainly in the conjugated form with glucuronic acid, and can be extracted from the urine by chloroform only after they have been hydrolysed with the enzyme β-glucuronidase. They can be separated from the crude chloroform extract by paper chromatography, and provide very suitable representative metabolites of cortisol, the specific activity or ^{14}C content of which can readily be determined, as they are relatively easily estimated by sensitive colour reactions.

Method

The radioactive cortisol was used as received from the National Institute of Health, Bethesda, U.S.A., without added carrier. Its stated specific activity was 1.47 mC per m.mol or 4.06 μC per mg. A small quantity of this was dissolved in pure ethanol and its ^{14}C content determined by direct plating of a small aliquot. The test dose was measured out by pipette and was diluted with 40 to 50 ml. of water. About 40 μg. was used in each test, equivalent to about 20,000 counts per minute (c.p.m.) in our counting system.

For the test the patient first empties the bladder and then drinks the whole test dose, taking care to avoid any loss. Urine is then collected for the next 24 hours. Two measurements are required from this sample: (1) a direct measurement of the total ^{14}C content of the 24-hour urine sample, and (2) determination of the specific activity of the tetrahydrocortisone.

Total ^{14}C content is determined by direct plating of 1- or 2-ml. samples of the urine on planchettes, counting for one to two hours and correcting for the weight of urine residue against a calibration curve specially constructed with varying quantities of urine. With the doses of radioactivity used counts are sometimes low, with consequent impairment of counting accuracy. In such cases accuracy can be improved by making a butanol extract of 5 to 10 ml. of urine and plating this on planchettes for direct counting. About 90% of the total ^{14}C is usually extracted in this way, and the contamination with inert material is much reduced. With these butanol extracts, however, greater care is needed to prevent creeping during plating.

^{14}C Content of the Tetrahydrocortisone

Liberation of the tetrahydrocortisone and tetrahydrocortisol from their glucuronide conjugates is achieved by incubating one-twelfth of the 24-hour sample—that is, two hours—with 500 units per ml. of a suitable β-glucuronidase preparation. Our own has been made from the livers of young rats by the method of Talalay, Fishman, and Huggins (1946). Incubation at *p*H 4.8 with acetate buffer for 48 hours at 37° C. liberates the tetrahydrocortisone. After incubation the steroids are extracted with chloroform by manual shaking. The chloroform extract is washed with a small volume of N/10 soda followed by water, and is then evaporated to dryness. The residue is transferred with a small volume of fresh chloroform to the starting line of a paper chromatogram and is developed for four days or more with the toluene/propylene glycol system of Burton, Zaffaroni, and Keutmann (1951) with a 20-μg. cortisol standard running in a separate lane. After drying the chromatogram thoroughly it is scanned for zones of radioactivity. Two large peaks are regularly found in the regions corresponding to tetrahydrocortisol and tetrahydrocortisone, which lie about 23 and 37% respectively of the distance from the starting line to the cortisol zone.

One or both of these zones are cut out, cut into small pieces with scissors, and eluted by standing the pieces overnight in a test-tube with 4 ml. of pure redistilled ethanol. Then 2 ml. of this eluate is plated on a planchette for ^{14}C counting, and 0.2 to 2 ml. of the remainder is assayed for reducing steroid by the method of Chen, Wheeler, and Tewell (1953), using tetramethylammonium hydroxide as the alkali. For the chemical analysis a paper blank of the same area from a part of the paper free of reducing steroid is also eluted and treated similarly.

From the results the specific activity of the tetrahydrocortisone is calculated and expressed as counts per minute per microgram of reducing steroid.

Calculation of the Cortisol Production Rate

If $S.A._U$ be the observed specific activity or ^{14}C content of the representative metabolite tetrahydrocortisone, and if C_U be the total ^{14}C content of the 24-hour urine sample, both expressed as counts per minute by the same counter, then the total mass of cortisol metabolites of all forms, known and unknown, in this urine will be $C_U/S.A._U$, provided only that the ingested radioactive steroid is handled in the body in the same manner as the endogenous cortisol.

If all the breakdown products of cortisol production were excreted ultimately in the urine, then under steady conditions of adrenal activity the mass of metabolites in the 24-hour urine would equal the daily production of cortisol. Such complete excretion of metabolites in the urine cannot, however, be assumed in the individual case. The efficiency with which the cortisol is actually excreted is, however, indicated in each case by the behaviour of the administered radioactive cortisol, for the ratio $C_U/\text{Dose} \times 100$ indicates the percentage excretion of cortisol metabolites during the 24 hours under observation.

Many factors are operative in determining the apparent excretion of orally ingested ^{14}C cortisol. Among these, loss of part of the dose or part of the urine sample, and impaired alimentary absorption, are factors which can give an apparent excretion efficiency lower than the true excretion of the endogenous cortisol metabolites. Since the magnitude of these factors will often be unknown, the true excretion efficiency must be presumed to lie between the observed figure C_U/Dose and the theoretical maximum of 100%. The estimate of the daily cortisol production will therefore lie between the two figures $\text{Dose}/S.A._U$ and $C_U/S.A._U$ dependent on the two extreme possibilities: (*a*) that the whole of the dose given was absorbed but that only a part was excreted in the urine, and (*b*) that only part of the dose was absorbed but that this was completely excreted in the urine. The mean of these two results will usually give a closer estimate than either extreme.

When it can be shown in the individual case that at least 80% of the dose administered has appeared in the 24-hour urine, then this provides satisfactory evidence that losses in absorption or of part of the urine sample have been of minor degree. It indicates, moreover, that the excretion

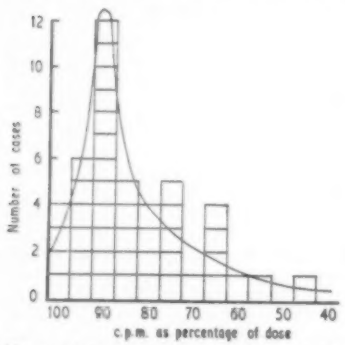
of metabolites is at least 80% complete, and thus should lead to an estimate of daily cortisol production which will lie between 80 and 100% of the true figure. The higher the observed recovery in a given case, the greater the accuracy of the estimate of cortisol production is likely to be.

Results

In a representative series of 12 normal subjects convalescent from diseases not likely to cause any adrenal stimulation, the mean recovery in the 24-hour urine sample was 87% of the ^{14}C of an administered dose of ^{14}C cortisol, the range being from 68 to 95 (Table I). In a larger series of 44 miscellaneous hospital patients, including some with endocrine disorders but excluding all those with gross renal functional damage, the mean excretion rate was 79% in 24 hours and 89% in 48 hours (see Chart). In 33 of these cases (72%) the excretion was in excess of 80% in 48 hours. The observed specific activity of the tetrahydrocortisone isolated from the 12 normal subjects ranged from 0.6 to 2.5 counts per minute per microgram in the normal group, with a mean of 1.5. These specific activities corresponded to estimated daily cortisol outputs which ranged between 4.9 and 25.3 mg., with mean of 12.8 mg. when based on a ratio $C_U/S.A._U$ and varied between 7.2 and 27.9 mg. per day when based on the ratio $Dose/S.A._U$, the mean then being 14.5 mg. (Table I). Though some of these outputs were much lower than had been expected the mean estimate of the group is in close correspondence with the clinical estimate based on replacement therapy in Addison's disease and after adrenalectomy.

TABLE I.—*Resting Normal Subjects*

Case No.	Dose (c.p.m.)	% Excretion 24 Hours	S.A.U	Estimated Cortisol Production between $C_U/S.A._U$ and Dose S.A.U (mg. day)	
1	19,500	95	1·3	14·2	15·0
2	19,500	92	2·4	7·5	8·1
3	17,200	78	1·8	7·5	9·5
4	18,100	86	0·65	24·0	27·9
5	27,500	95	1·2	21·8	23·0
6	18,000	68	2·5	4·9	7·2
7	16,700	84	1·1	12·7	15·2
8	18,000	82	1·6	9·2	11·2
9	18,000	95	1·17	14·6	15·4
10	16,400	87	1·2	11·9	13·6
11	19,370	88	2·0	8·5	9·7
12	18,300	92	1·03	16·4	17·8
	Mean ..	87	1·50	12·8	14·5



Total urinary excretion in 48 hours of ^{14}C after an oral dose of ^{14}C cortisol. Each square represents the excretion in one of the 44 cases.

In each of five subjects comparison was made of cortisol output estimates obtained on one occasion by oral and on another by intravenous administration of the ^{14}C cortisol. The mean of the estimates by the oral route was 8.1 mg. and the mean of those obtained by the intravenous injection 9.8 mg. This comparison thus suggests that no significant error is introduced by giving the ^{14}C cortisol into the portal blood stream.

In a series of 12 tests on persons undergoing adrenal stimulation by corticotrophin the mean recovery of the administered ^{14}C was 76.4% in 24 hours. Estimates of cortisol production varied from 21.8 to 257 mg. per day, with a mean output of 127 mg. daily estimated by the ratio $Dose/S.A._U$ and of 99 mg. when estimated from $C_U/S.A._U$ (Table II). In this series no attempt was made to achieve maximum stimulation, and higher outputs could no doubt have been achieved with larger doses of corticotrophin.

TABLE II.—*Corticotrophin Stimulation*

Case No.	Dose (c.p.m.)	% Excretion 24 Hours	S.A.U	Estimated Cortisol Production between $C_U/S.A._U$ and Dose S.A.U (mg. day)	
25	19,100	84	0·2	82	97·5
26	17,600	87	0·08	192	225
27	18,100	70	0·32	39·6	56·6
28	18,000	72	0·23	59·5	83
29	18,000	77	0·26	53	69
30	18,000	77	0·07	207	257
31	18,000	75	0·62	21·8	29
32	18,000	66	0·1	119·5	180
33	16,400	74	0·09	135	182
34	18,400	89·5	0·11	150	167
35	18,400	58	0·21	49	86
36	18,400	88	0·21	77	88
	Mean ..	76·4	—	99	127

In contrast, a series of four cases of gross hypoadrenalism due to hypopituitarism or Addison's disease gave a mean 24-hour recovery of ^{14}C of 81% of the dose and indicated a mean daily cortisol production of between 0.8 and 1 mg. A similar low output of only 1 mg. daily was recorded in an adult subject with pseudohermaphroditism due to adrenal hyperplasia whose treatment with cortisone had been temporarily suspended (Table III).

TABLE III.—*Hypoadrenalism*

Case No.	Disease	Dose (c.p.m.)	% Excretion 24 Hours	S.A.U	Estimated Cortisol Production between $C_U/S.A._U$ and Dose S.A.U (mg. day)	
37	Addison's	16,280	87·5	20	0·7	0·8
38	Hypopit.	27,500	84	24	1·0	1·1
39	..	16,800	72	20·7	0·6	0·8
40	..	18,400	81	15·0	1·0	1·2
41	Pseudoherma-phroditism	18,400	84	17·2	0·9	1·07
		Mean..	81·7	—	0·8	1·0
	Inhibition with					
43	9-α-Fluoro-cortisol	17,200	82	7	2·3	2·8
44	Prednisone	27,500	92	10·6	2·4	2·6
45	..	18,400	72	8·5	1·56	2·16
		Mean..	82	—	2·09	2·52

With the method proposed here it is sometimes possible to estimate cortisol output in persons whose adrenal activity is inhibited by prednisone or other similar steroid. When prednisone is given, a large part of it is converted into prednisolone and appears as such in the urine. Most of this can be removed by an initial chloroform extraction before treatment with glucuronidase, but small amounts may persist in the glucuronidase extract and will run on the chromatogram at a rate similar to that of tetrahydrocortisone, so that a proper separation of the two is not readily achieved. But no such contamination occurs with the tetrahydrocortisol, which can therefore sometimes be used to determine the specific activity of the metabolites. In three subjects on prednisone in whom cortisol production rate was measured in this way outputs of 2 to 2.8 mg. were recorded (Table III). However, Caspi and Pechet (1957) have identified tetrahydrocortisol among the metabolites of prednisone, so that estimates based on the specific activity of tetrahydrocortisol in persons on prednisone may be too high. The actual outputs in the three cases studied will probably therefore be below the recorded figures.

It is now well recognized that in many active disease states adrenal stimulation often occurs. In a series of six such cases estimates of cortisol production varying from 10 to 31.9 mg. daily were recorded, the mean production rate being between 18.1 and 22.2 mg. daily. In three further subjects with well-marked hyperthyroidism the mean estimated cortisol production lay between 21.9 and 25.3 mg.

daily. In three subjects with advanced hepatic cirrhosis but without ascites the mean estimates were between 6.7 and 9.5 mg. daily (Table IV).

TABLE IV.—*Disease States*

Case No.	Disease	Dose (c.p.m.)	% Excretion 24 Hours	S.A./v	Estimated Cortisol Production between C./S.A./v and Dose/S.A./v (mg./day)	
			Active Diseases			
13	Lymphosarcoma	18,500	86	0·7	22·7	26·4
14	Carc. breast	19,200	84	1·3	12·4	14·7
15	Rheum. fever	17,200	90	1·0	15·5	17·2
16	Advanced tuberculosis	19,100	81	0·6	25·8	31·9
17	Advanced Hodgkin's	18,000	58	1·04	10·0	17·3
18	Rheum. fever	18,000	86	0·69	22·4	26·0
			Mean		18·1	22·2
			Hyperthyroidism			
19		17,600	99	1·02	17·1	17·3
20		18,100	94	0·65	26·1	27·9
21		18,100	73	0·59	22·4	30·7
			Mean		21·9	25·3
			Hepatic Cirrhosis (with Endocrine Change)			
22		16,800	84	2·3	6·1	7·3
23		16,800	54	1·5	6·1	11·2
24		18,000	79	1·8	7·9	10·0
			Mean		6·7	9·5

Discussion

The calculation of the cortisol production rate proposed here involves two stages. First is the estimation of the total mass of adrenal cortisol metabolites in the urine. The reliability of this depends solely on the entry of the ^{14}C of the ^{14}C cortisol equally into all the metabolites. Although this has not been strictly shown, except in a few instances (Cope and Black, 1958), it is difficult to see why it should not be so, since ^{14}C cortisol must be treated in the body precisely as endogenous cortisol. The dose administered will not appreciably alter the prevailing concentrations in the blood, since it represents a quantity normally to be found in less than 500 ml. of venous blood.

The second stage is the determination of the relation between the total mass of excreted metabolites in the urine and the actual cortisol production. For this also the behaviour of the ^{14}C provides the necessary information of the proportion excreted in the urine. The excretion observed in the 24-hour urine sample is less than the total excretion, since further small amounts are excreted during the second 24 hours. With the small dose of ^{14}C cortisol used here it is difficult to measure reliably the ^{14}C content of the second 24-hour urine sample, but it usually contains about 5% of the dose.

Administration of the ^{14}C cortisol by the oral route introduces certain ambiguities about the completeness of absorption, and the absorbed cortisol enters the portal blood stream. Intravenous administration of the dose would avoid the possible objection that steroid entering the portal blood is not necessarily treated in the same manner as cortisol in the systemic circulation, and would, furthermore, eliminate uncertainty over the completeness of absorption. We have preferred the oral route, however, because it is simpler, because in most cases absorption is rapid and complete (Peterson and Wyngaarden, 1956), because it is likely to give a slow and steady introduction of the dose into the blood stream, and because it avoids psychological trauma which may readily cause an adrenal stimulation. We have not found it easy to be sure of the correct introduction of the whole dose intravenously without using a prolonged saline drip which may upset the patient and his adrenal activity. The relatively good correspondence we have obtained between estimates of cortisol production based on oral and intravenous ^{14}C cortisol administration justifies the belief that the oral route, with its greater simplicity, introduced no systematic errors.

Because of the uncertainty which will frequently exist over the completeness of ingestion or of absorption of the dose, or over the completeness of the 24-hour urine specimen, the estimate of output must be a range of values based on the two extreme possibilities mentioned earlier. But in the majority of cases studied, in which an excretion of over 80% of the dose can be demonstrated, the two estimates will not be widely separated, and a mean of the two should reduce the maximum error due to this ambiguity to little more than 10%.

Because the specific activity of the cortisol metabolite and not its total amount is the measurement required, only total urine ^{14}C and the final analysis of the eluate from the chromatogram need to be accurate. Losses in extraction of the urine, inadequate hydrolysis of the glucuronide, losses during transfer of the steroid extract to the paper chromatogram, and incomplete elution from this chromatogram will not at all impair the accuracy of the test.

The demands made by the method on the technical skill of laboratory staff are therefore relatively small.

The method measures the actual output during the 24 hours and not the production rate for a short period. For its principle to be valid a reasonably steady state must prevail, and it is not suited to the measurement of rapid changes in output either during the day or from day to day.

The validity of the method is dependent on the ability to obtain the tetrahydrocortisone sufficiently free from interfering impurities. Although no attempt is made to isolate this metabolite in a state of chemical purity, evidence that the relatively simple technique employed here yields a product pure enough for clinical purposes has been presented elsewhere (Cope and Black, 1958).

Previous attempts to estimate the daily cortisol production rate are summarized in Table V.

TABLE V

Authors	Method	Circumstances	Output Daily (mg.)
Knowlton (1952) ..	Replacement therapy	Normal	12·5–25
Dorfman (1954) ..	? Excretion of metabolites	,,	Men 21. Women 18
Silber (1955) ..	17-OHCS excretion	,,	30–60
Bondy and Altrock (1953)	Adrenal vein F	Stress	21
Moxham and Nabarro (1956)	17-KGS excretion	Normal	Men, 8·5 to 49 Women, 5·5 to 40
	17-OHCS excretion	,,	Men, 14 to 45 Women, 9·5 to 36
Samuels *et al.* (1957)	Rate fall blood F	Normals	36
		Corticotrophin	250
Peterson and Wyngaarden (1956)	Fall of S.A. blood F	Normals	17 to 29
		Evening	12
		Corticotrophin	160
Hardy and Turner (1957)	Adrenal vein F	Stress	34
Cope and Black (1958)	S.A. of tetrahydrocortisone	Normals	5 to 25
		Corticotrophin	Up to 257

The needs of the Addisonian or adrenalectomized subject, which vary from 12.5 to 25 mg. daily, suggest an output from the normal adrenal of this order. Several attempts have been made to correlate the excretion of certain groups of cortisol metabolites with the actual production rate, by observing the proportion of an ingested dose which is subsequently excreted in the form of such groups of compounds. Dorfman (1954) and Silber (1955) have made estimates in this way, that of the former being 18 to 21 mg. and of the latter the much higher figure of 30 to 60 mg. daily. Moxham and Nabarro (1956) have correlated oral cortisol dosage with both ketogenic steroid and 17-hydroxycorticosteroid excretion, and have thereby provided data which suggest an excretion between 5.5 and 49 mg. judged by ketogenic steroids and from 9.5 to 45 mg. judged by the 17-hydroxycorticosteroids. The disadvantage of such estimates is that one must assume that the observed average

ratio between cortisol dose and the metabolite will apply to each individual case, an assumption which is scarcely justified in disease states.

Both Bondy and Altrock (1953) and Hardy and Turner (1957) have obtained much more direct estimates in selected individuals by actual collection and analysis of the adrenal vein blood. This is clearly a procedure of very limited application and will inevitably introduce a condition of stress which is likely to raise the adrenal activity.

The rate of disappearance of injected cortisol has been employed by Samuels *et al.* (1957) to estimate cortisol destruction rate, but when cortisol levels in the blood are greatly raised there is considerable likelihood that the turnover rate or destruction rate will be increased. It is for this reason especially that the radioactive steroid is preferable, for it permits the use of quantities so small that the blood levels do not exceed the normal physiological range.

The method of Peterson and Wyngaarden (1956) is especially suited to estimates of cortisol turnover during relatively short periods, but is not well suited to observational periods greater than a few hours. For general clinical purposes, however, an average excretion rate over at least a day is likely to be of much more diagnostic value, and that is more conveniently obtained by the method used in the present paper.

The estimates of cortisol production obtained by our method, with a mean of 13 to 14 mg. daily, are appreciably lower than the estimates obtained by Peterson and Wyngaarden (1956), which are the only comparable estimates of which we are aware. Their results, with a mean output of 21 mg. daily, are, however, based on data obtained in a three-hour period during the morning hours when there is a strong probability that adrenal cortical activity is at the higher levels of the diurnal rhythm, and are based on the assumption that the observed adrenal activity continues throughout the 24 hours, which is improbable. In contrast the estimates obtained here are the result of observation of the whole 24-hour period, and include the period of sleep when probably adrenal activity is at its lowest. It is of considerable interest in this connexion that in the one case where Peterson and Wyngaarden made their test at 9 p.m. instead of in the morning they obtained their lowest estimate of cortisol production rate, an output of 12 mg. daily, and this figure is in good agreement with our own average.

The wide variation in outputs of cortisol in patients on corticotrophin is of considerable interest, for all were subjects on corticotrophin therapy of normal dosage for the treatment of disease. In one case no appreciable stimulation had been achieved; in other cases a fifteenfold increase in output had occurred. The higher outputs are comparable in magnitude to estimates made in single cases by Samuels *et al.* (1957) and by Peterson and Wyngaarden (1956). They do not represent the highest attainable outputs.

Unlike most estimates and analyses of endocrine function, the accuracy of this test is not appreciably reduced at the lower levels of adrenal activity. The amount of ^{14}C to be found in the final eluate is dependent on the dose of ^{14}C cortisol administered, and is not at all affected by the degree of adrenal activity. In persons with very low adrenal activity the amount of tetrahydrocortisone in the urine is greatly reduced, but sufficient for analysis can usually be obtained by increasing the volume of urine extracted after glucuronidase hydrolysis.

Because of this undiminished sensitivity at the lower levels of activity, the method is likely to be of special value in determining the severity of cases of hypopituitarism. Thus outputs of less than 1 mg. daily in cases of complete hypopituitarism can be distinguished from outputs between 2 and 5 mg. which have been found in less complete hypopituitarism. This ability to measure low cortisol outputs has already proved of some clinical value in assessing the degree of pituitary damage produced by irradiation of the gland with yttrium implants in the treatment of metastatic carcinoma.

The outputs in hyperthyroidism are all at the upper limit of the quiescent normal range. They are not surprising in view of the increased metabolism which occurs in such subjects.

The figures recorded in cirrhosis, however, suggest that output in severe liver damage is reduced to 50 to 60% of the normal. Samuels *et al.* (1957) have also obtained evidence suggesting that turnover in hepatic cirrhosis is reduced. This may be due to slower destruction of the hormone by the liver, so that less fresh cortisol is needed to maintain normal plasma concentrations.

Summary

A method has been developed, using ^{14}C-labelled cortisol, for measuring the daily production rate of cortisol by the adrenal cortex in man.

In 12 quiescent and convalescent subjects, free of endocrine or other active disease, the range of estimated production rates was from 4.9 to 27.9 mg. daily, the mean figure being 12.8 or 14.5 mg. daily according to the method of calculation.

In six subjects with severe active but non-endocrine diseases values of 10 to 31.9 mg. were estimated, with a mean of 20.1 mg. daily.

The response to routine corticotrophin therapy was very variable, the highest estimated output being about 257 mg. daily and the lowest 21.8 mg., a figure within the normal unstimulated range.

In three subjects with advanced hepatic cirrhosis production rates were low, averaging 8.1 mg. daily; and in three patients with hyperthyroidism the cortisol production rates were high, averaging 23.6 mg. daily.

In hypoadrenalism due to Addison's disease or to hypopituitarism estimated cortisol production rates were between 0.6 and 1.2 mg. daily, with a mean of 0.9 mg., and in three subjects whose adrenals were inhibited by prednisone or 9-α-fluorocortisol therapy estimated production rates averaged 2.3 mg. daily. A cortisol production of only 1 mg. daily was found in a pseudohermaphrodite, confirming the low output believed to occur in these patients.

Our thanks are due to the Medical Research Council for a grant to one of us (E. B.), and to the United States National Institutes of Health, Division of Research Grants, for a generous gift of ^{14}C-labelled cortisol. We are grateful also to Miss Olwen Jenkins and Miss Sylvia Hughes for valuable technical assistance.

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The 37th annual meeting of the British Cardiac Society was held at Leeds University on April 17 and 18, under the chairmanship of Dr. JOHN TOWERS. On the first day there were short papers followed by demonstrations in the afternoon, and a symposium on extracorporeal circulation, in which Professor A. C. BROM, of Leyden, and Dr. L. R. RADIGAN, of Indianapolis, took part as guest speakers. On the second day there was a symposium on diuretics followed by more short papers. The annual dinner was held in the university refectory, with Dr. Towers in the chair.

THORACIC ACTINOMYCOSIS

BY

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Since Zachary Cope (1938) wrote his classic monograph on actinomycosis, considerable advances in the understanding of the pathogenesis of this disease have been made. We wish to present brief reports of two cases of thoracic actinomycosis illustrative of these advances, both of which were initially entirely unsuspected. Pleuritic pain was the presenting symptom in one and a "rheumatism" of the shoulders in the other. Weight loss and polymorphonuclear leucocytosis were common to both.

Actinomycotic infection is not a rare condition, nor is its incidence confined to farmers or horse dealers. Favourable response to antibiotics is another cogent reason for considering it high on the list of possibilities in the differential diagnosis of any obscure infective condition. When overlooked it can give rise to distressing and protracted disability, often with an eventual unhappy outcome, but if diagnosed early and treated correctly there is every justification for optimistic prognosis.

Case 1

A 47-year-old car salesman was admitted to Westminster Hospital on February 5, 1948, with a four-weeks history of cough, fever, and pleuritic pain.

Chest radiograph showed collapse and consolidation of the right lower lobe, with an overlying encysted effusion (Fig. 1). The erythrocyte sedimentation rate (E.S.R.) was 49 mm. in first hour (Wintrobe); Hb 88% (13 g./100 ml.); leucocytes, 12,000 per c.mm. (87% polymorphs). Tubercle bacilli were not found in the sputum by microscopy or culture. Three successive pleural taps produced yellow turbid fluid which contained polymorphs but was sterile on aerobic culture. Blood cultures (aerobic and anaerobic) were negative. Two weeks after his admission clubbing of the fingers was observed. Sulphadimidine and penicillin were given but discontinued after one week, having failed to influence the pyrexia. This latter subsided spontaneously over the next month, and the size of the pleural effusion diminished concurrently. The patient was discharged after 10 weeks—pending admission to a sanatorium—with a small residual effusion and a provisional diagnosis of pulmonary tuberculosis. When reviewed as an out-patient three months later he had improved and had gained nearly a stone (6.4 kg.) in weight, but his fingers were still clubbed and residual signs at the right base persisted.

He was not seen again until seven years later (1955), during which time he had been fully active. His new complaint, of four months' duration only, was of lassitude and loss of over a stone (6.4 kg.) in weight. He was thin and obviously ill, but afebrile. Gross clubbing of the fingers was present together with physical signs of a right pleural effusion. Chest radiograph revealed a curious and, we think, characteristic type of osteitis of the posterior portions of the fourth to sixth ribs (Fig. 2) in addition to an effusion. E.S.R. 50 mm. in first hour (Wintrobe); leucocytes, 12,000 (90% polymorphs). Paracentesis yielded thick yellow pus, containing many polymorphs and Gram-positive branching rods. After seven days' anaerobic incubation *Actinomyces israeli* was cultured, and the same organism was recovered from the sputum.

Heavy albuminuria and a urea clearance only 56% of normal indicated renal damage and a congo-red absorption of 70% within 30 minutes suggested amyloidosis. This possibility was supported by the finding of splenomegaly.

Six mega units of penicillin was given daily, and continued for three weeks, concurrently with two four-day courses of intramuscular streptomycin, 1 g. a day. At the end of this time rib resection was performed under local analgesia and a thick-walled empyema drained. On the following day the patient felt extremely weak and his temperature fell

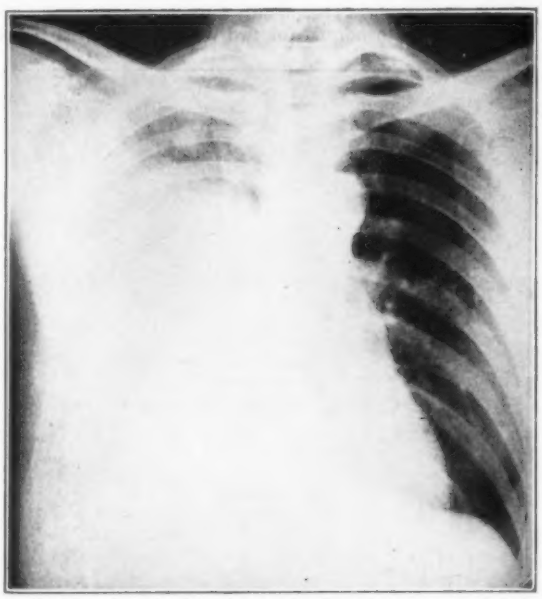

FIG. 1.—Case 1. P.A. chest radiograph February 6, 1948.

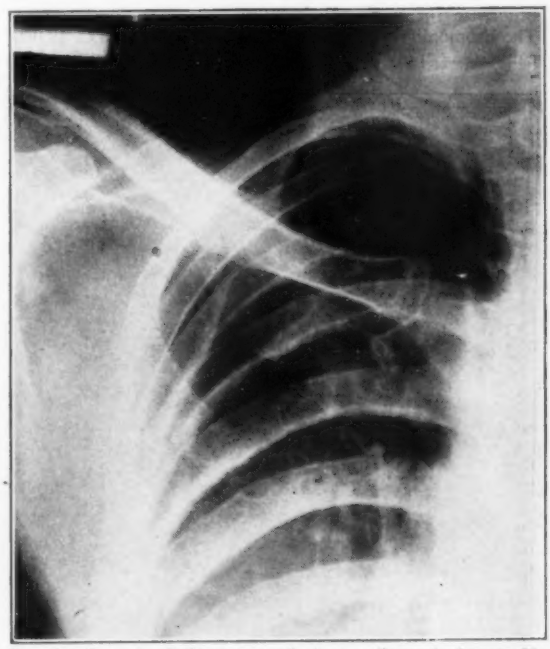

FIG. 2.—Case 1. Enlargement of chest radiograph August 29, 1955, to show right upper ribs.

dramatically from normal to 95° F. (35° C.) at which level it remained for five days. Two days later a sudden clinical deterioration was accompanied by a fall in blood pressure to a level of 70/50 mm. Hg., and the serum electrolytes confirmed the clinical impression of adrenal failure (sodium, 125 mEq/l.; potassium, 5.9 mEq/l.; chlorides, 88 mEq/l; blood urea, 114 mg./100 ml.). Intravenous infusion containing noradrenaline and 200 mg. of hydrocortisone, supplemented intramuscularly by 200 mg. of cortisone and 20 mg. of deoxycortone acetate, failed to stem his deterioration, and he died the following day.

Post-mortem Examination.—There was a chronic empyema in the right chest, measuring approximately 3½ in. (9 cm.) in diameter. Histological examination of the lung revealed non-specific chronic inflammation only. The liver and spleen were moderately enlarged, and showed amyloid reaction, as did the pancreas, adrenals, and kidneys. On histological examination of the adrenal glands the cortex was found to be almost completely replaced by amyloid substance.

Comment.—The case was almost certainly initially suffering from actinomycotic infection, and the later finding of extensive amyloidosis was presumably consequent upon its long-standing presence. In the final stages, failure to appreciate the significance of hypothermia as indicative of adrenal insufficiency delayed substitution therapy, which otherwise might well have altered the outcome. One interesting feature was the characteristic type of rib osteitis, giving an almost diagnostic radiological appearance.

Case 2

A man aged 49 first presented in the out-patient department of Westminster Hospital in November, 1956. He had experienced a dull interscapular pain for three months which extended into the upper arms and eventually forced him to discontinue work. He admitted to a slight unproductive cough, some nocturnal dyspnoea and sweating, also to a weight loss of 2 stone (12.7 kg.). On examination he was obviously ill, febrile—102° F. (38.9° C.)—and severely anaemic. There was a subcutaneous, fluctuant, but painless swelling 4 in. (19 cm.) in diameter over the upper dorsal spine, and the overlying skin was not inflamed. Bronchial breathing was audible in the left upper zone anteriorly, but otherwise the chest was free of abnormal physical signs. The haemoglobin was 58% (8.5 g./100 ml.); W.B.C. 18,000/c.mm. (86% polymorphs), and E.S.R. of 65 mm. in first hour (Wintrobe). The chest radiograph showed a homogeneous opacity at the left apex, the rib shadows being normal (Fig. 3). Radiography of the dorsal spine revealed a loss of definition and rarefaction of the bodies of D 1—4 vertebrae (Fig. 4). The abscess was aspirated and 20 ml. of brown blood-stained pus containing "sulphur granules" withdrawn. Microscopy showed many neutrophils, Gram-positive branching filaments, and a moderate number of Gram-negative bacilli. Culture yielded a growth of *A. israeli* and *Actinobacillus actinomycetem comitans*. Neither of these organisms, nor any tubercle bacilli, were isolated from the sputum.

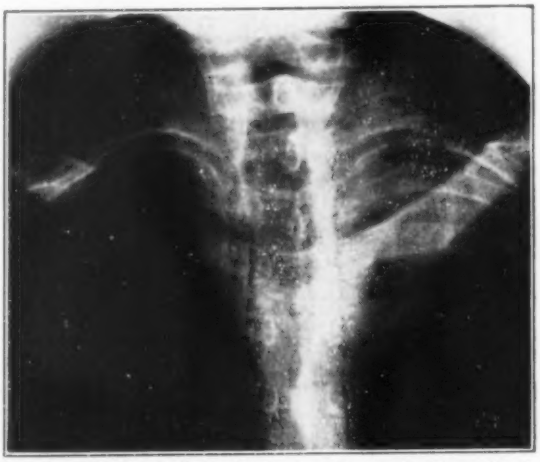

FIG. 4.—Case 2. Radiograph of upper dorsal spine December 5, 1956.

Six mega units of penicillin was given intramuscularly daily for seven weeks, together with four courses of intramuscular streptomycin, 1 g. a day for four days at fortnightly intervals. Aspiration of the abscess was repeated frequently, and 1 mega unit of penicillin was instilled on each occasion. Fourteen days after treatment the pus became sterile, and after 28 days no organisms could be demonstrated in the smear. Steady clinical improvement was evidenced by a return of appetite and gain of 13 lb. (5.9 kg.) in weight. The initially high fever fell rapidly but did not return to normal for two weeks. The chest radio-

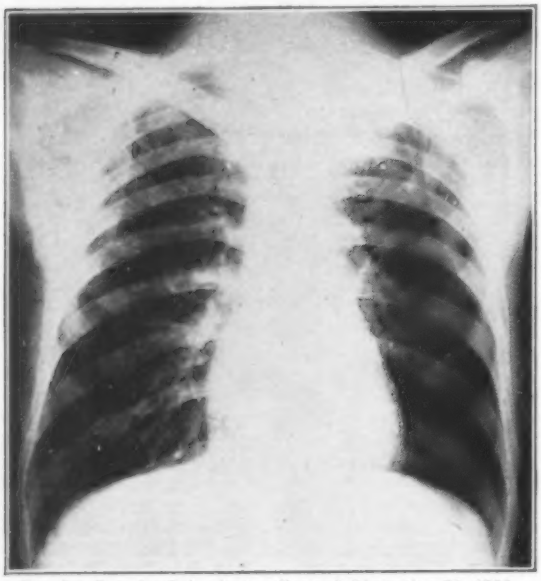

FIG. 3.—Case 2. P.A. chest radiograph November 23, 1956.

FIG. 5.—Case 2. P.A. chest radiograph April 23, 1957.

graph showed little change but the appearances of the upper dorsal spine were much improved. He was discharged to convalescence eight weeks after admission.

Four weeks later, although symptom-free, the chest radiograph showed a new opacity in the right second interspace and the left mid-zone (Fig. 5). There was neither pyrexia nor any abnormal physical signs. E.S.R. was 21 mm. in first hour (Wintrobe). Treatment with intramuscular penicillin and streptomycin was given as before for six weeks. The chest radiograph taken at the end of this course showed clearing of both lung fields. He was then given oral phenoxymethylpenicillin, 120 mg., three times a day, on which dose he continued.

Comment.—The infection in this instance was either pulmonary or mediastinal, involving the upper dorsal vertebrae and presenting as a cold abscess over the back of the neck. Bilateral intrapulmonary recrudescence following within four weeks of cessation of antibiotic therapy emphasized the necessity for a prolonged follow-up period.

Discussion

Types of Thoracic Actinomycosis.—These have been classified by Cope (1938) into bronchial, parenchymal, and mediastinal. The first type is rare, with slight symptoms, bronchitis, and actinomyces in the sputum. Parenchymal disease begins generally in the lower lobes with eventual involvement of the remaining lung. Fascial planes are ignored, but lymph nodes and lymphatics are seldom invaded. The pleura shows little resistance, with early effusion, becoming purulent and progressing to empyema formation (Barker, 1954) as in our Case 1. Infiltration of the thoracic wall follows, with an overlying abscess at the dependent part of the pleural cavity. The mediastinal type more readily invades the thoracic wall, with consequent early abscess formation. Pleural effusion and empyema are equally early features. The bodies of the thoracic vertebrae are often involved, as in Case 2.

Bacteriology.—*A. israeli* has long been considered the sole causative organism. In 1878 Israël found coccoid formation in the "sulphur granules" of actinomycotic pus. He thought these were a developmental phase of the fungus. Wright (1905) described the frequent presence of other bacteria often intimately associated with the substance of granules. He believed that sometimes the accompanying bacteria play an important part in the extension of the disease. Klinger (1912) found a Gram-negative aerobic coccobacillus in 5 out of 12 cases. He called this organism *Bacillus actinomycetem comitans*, and subsequently it has been noticed in association with actinomycosis (Colebrook, 1920; Bayne-Jones, 1925; Bates, 1933; Goldsworthy, 1938; Clemens, 1940). Holm (1950) found "other organisms," including this actinobacillus, in the pus from 650 closed actinomycotic lesions. The type of organism varied with the site affected, but in thoracic lesions the actinobacillus was usually present. Also the actinobacillus has been found only in cases of actinomycosis. Colebrook (1920) discussed the significance of this organism, but was unable to find a satisfactory explanation. Holm (1950) believes that actinomycosis is a multiple infection arising from a synergism between *A. israeli* and associated organisms. In this respect it would resemble other infections where there is an association between anaerobic and aerobic organisms—for example, gas-gangrene (clostridia and coliforms). We feel that the actinobacillus is significant and plays an important part in the establishment and continuation of the actinomycotic infection.

Mode of Entry.—In 1920 Colebrook stated that the established idea that the ray fungus is conveyed to man from vegetable sources—for example, grasses, soil, etc.—should be viewed with considerable scepticism. It is now generally accepted that *A. israeli* is not the same species as *A. bovis* of cattle actinomycosis nor the species, usually aerobic, found in grasses and soils (Wright, 1905; Cope, 1938; Rosebury, 1944; Weed and Baggenstoss, 1949). *A. israeli* is often found in carious teeth and infected tonsils of normal people (Naeslund, 1925; Davis, 1941; Slack, 1942). It probably requires trauma or locally reduced resistance, with an associated synergic aerobe, to establish a lesion. Pulmonary infection may originate by: inhalation, penetration of the oesophagus, extension from the cervical region via the mediastinum, or retroperitoneal extension from below the diaphragm.

Osteitis.—Infection of bone usually occurs either primarily, as in the jaw, or by extension from neighbouring tissue. Infection by the blood stream is rare, but may cause a lesion in the long bones. In vertebrae involved by local extension of the disease there is, radiologically, irregular rarefaction of the body and surrounding osteosclerosis; angular collapse is rare, and the intervertebral disk is not attacked (Lubert, 1944; Shanks and Kerley, 1950). In the ribs a similar process occurs, the earliest change being a periostitis as in Case 1. This gives an interesting and, we feel, characteristic radiological appearance of considerable diagnostic importance.

Treatment

The sensitivity of *A. israeli* varies *in vitro* (Strauss *et al.*, 1951), but it has been found that the majority of strains are sensitive to less than 0.5 microgram (approximately 0.75 unit) per ml. of penicillin (Garrod, 1952). The *Actinobacillus actinomycetem comitans* is normally insensitive to penicillin but sensitive to streptomycin, as in our Case 2. For this reason both antibiotics were given. In spite of 6 mega units of penicillin daily for seven weeks and two courses of streptomycin, 1 g. daily for four days, new lesions appeared in both lungs one month after cessation of therapy. The failure of some cases to respond to adequate penicillin therapy may be due to insufficient antibiotic reaching the lesion, as a result of avascularity and fibrosis. This may well occur in actinomycotic involvement of bone. Fisher and Harvey (1956) suggest continuation of penicillin treatment for six months, but this would seem necessary only in recurrent or advanced cases. In these, after initial systemic therapy, continuation with oral penicillin would probably be adequate.

Summary

Two cases of thoracic actinomycosis are reported. The first of these patients presented with a pleural effusion and died seven years later of adrenal failure due to amyloidosis. The second presented with an empyema necessitatis pointing high in the interscapular region.

The diagnostic importance in thoracic actinomycosis of what we feel to be a characteristic type of osteitis of the ribs is emphasized.

The significance of organisms other than *Actinomyces israeli*, particularly *Actinobacillus actinomycetem comitans*, in the pathogenesis of the disease is discussed.

In order to deal effectively with both organisms treatment with penicillin and streptomycin is suggested, and in some cases prolonged therapy may be required.

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SOME EFFECTS OF SODIUM SALICYLATE ON MUSCLE METABOLISM

BY

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Reid, Macdougall, and Andrews (1957) have demonstrated anew that aspirin (acetylsalicylic acid) is capable of reducing hyperglycaemia, glycosuria, and ketonaemia in some diabetic patients. In the rat, both aspirin and sodium salicylate are capable of reducing glycosuria and hyperglycaemia in diabetes induced by partial pancreatectomy with forced feeding (Ingle, 1950), alloxan (Smith, Meade, and Bornstein, 1952), or cortisone (Smith, 1952). The mechanism of this action of salicylate is not known. Salicylate is unlikely to act in diabetes by reducing gluconeogenesis, for in normal rats salicylate treatment produces negative nitrogen balance (Winters and Morrill, 1955), and it does not reduce the negative nitrogen balance of diabetes induced in rats with cortisone (Smith, 1952).

Smith and Jeffrey (1956) found that salicylate slightly inhibited the uptake of glucose by the isolated rat diaphragm, an observation which would seem to indicate that salicylate does not increase the utilization of glucose by muscle. However, the experiments of Smith and Jeffrey were carried out with diaphragm incubated in a phosphate-buffered medium. Randle (1956) and Randle and G. H. Smith (unpublished) have observed that oxygen lack and a number of compounds which interfere with the oxidative production of energy-rich phosphate promote the uptake of glucose by diaphragm incubated in a medium buffered with bicarbonate, but not in a medium buffered with phosphate. Since salicylate is also believed to interfere with the oxidative production of energy-rich phosphate (Meade, 1954; Smith and Jeffrey, 1956; Brody, 1956; Penniall, 1956), it seemed important to reinvestigate the effect of salicylate on the uptake of glucose by diaphragm in a medium buffered with bicarbonate.

When isolated rat diaphragm is incubated in the presence of a ^{14}C-labelled amino-acid, ^{14}C is incorporated into the protein of the diaphragm (Sinex, MacMullen, and Hastings, 1952; Krahl, 1953; Manchester and Young, unpublished). Since salicylate treatment produces negative nitrogen balance in the intact rat it was of interest also to investigate its influence on the incorporation of [^{14}C]amino-acids into the protein of the isolated diaphragm.

Methods

Diaphragm.—The preparation and incubation of diaphragm were as described by Randle (1956).

Media.—Bicarbonate-buffered medium (Gey and Gey, 1936), gassed with O_2 + CO_2 (95:5), *p*H 7.4 at 37° C. Phosphate-buffered medium (Krebs–Ringer phosphate, after Umbreit, Burris, and Stauffer, 1949), gassed with O_2, *p*H 7.4 at 37° C. Glucose was added to give a concentration of 2.5 mg./ml. The radioactive amino-acids [1-^{14}C]glycine and uniformly labelled L-[^{14}C]glutamic acid and L-[^{14}C]lysine were present at a concentration of about 0.1 μmol./ml. and a specific activity of about 50 μC./mg. Sodium salicylate was added to yield a concentration of 5×10^{-3}M. Crystalline insulin (Boots) was dissolved in N/300 HCl to 20 units/ml. and diluted with medium to 0.1 unit/ml.

Glucose uptake was measured by the disappearance of glucose from the medium when one hemidiaphragm was incubated in each flask for 1 hour in 1 ml. of medium. Glucose was estimated either by the Somogyi (1945) modification of Nelson's method or by the method of Huggett and Nixon (1957). Glucose uptake was calculated as milligrams of glucose disappearing from the medium per gramme of wet diaphragm per hour of incubation. Potassium loss from the diaphragm was measured by the change in potassium content of the medium during incubation. Potassium was estimated by flame photometry. Potassium loss was calculated as micro-equivalents of potassium added to the medium per gramme of wet diaphragm per hour of incubation.

Total muscle water was determined by weighing the diaphragm wet and after freeze-drying.

Thiosulphate, glucose, and xylose spaces were determined with the whole diaphragm preparation of Kipnis and Cori (1957), a preparation in which muscle attachments to rib and vertebral column are intact. The diaphragm was incubated for one hour in 10 ml. of medium containing (for glucose and thiosulphate space) glucose 2.5 mg./ml. and sodium thiosulphate 20 mEq/l., or (for xylose space) D-xylose 1.5 mg./ml. and glucose 1 mg./ml. At the end of incubation glucose or thiosulphate or xylose was determined in diaphragm muscle and medium. The space for thiosulphate, xylose, or glucose was calculated from the formula (space = quantity in muscle/concentration in medium). Muscle extracts and medium were deproteinized with tungstic acid for thiosulphate determination and by the method of Somogyi (1945) for glucose or xylose determinations. Thiosulphate was determined in muscle extracts or medium by the method of Newman, Gilman, and Philips (1946), glucose by the method of Huggett and Nixon (1957), and xylose by the method of Roe and Rice (1948).

Uptake of ^{14}C into Diaphragm Protein.—Two hemidiaphragms were incubated together in 2 ml. of medium in each flask for two hours. After incubation the diaphragm was homogenized in trichloroacetic acid (T.C.A.) and the precipitate collected and heated in T.C.A. for 15 minutes at 90° C. The insoluble material was treated twice with 0.4 N NaOH and the dissolved protein then reprecipitated from the NaOH extract with T.C.A., washed with ethanol-ether (50:50), ether, and dried in a vacuum desiccator. The dried sample of protein was ground in a mortar, collected on a 1 sq. cm. plastic planchette, and counted as an infinitely thick sample (Popják, 1950).

Results

Salicylate and Glucose Uptake.—In a medium buffered with bicarbonate, sodium salicylate (5×10^{-3}M.) added *in vitro* increases the uptake of glucose by isolated diaphragms from intact rats (Table I). The concentration of salicylate used is about the same as the blood level of salicylate in the diabetics treated with aspirin by Reid *et al.* (1957). Sodium *p*-hydroxybenzoate, unlike salicylate (*o*-hydroxybenzoate), does not increase glucose uptake.

In a phosphate-buffered medium sodium salicylate does not stimulate glucose uptake. This confirms the earlier observation of Smith and Jeffrey (1956).

Salicylate and the Glucose and Xylose Spaces.—Sodium salicylate *in vitro* does not significantly alter the total water or the thiosulphate space of the isolated rat diaphragm. It may therefore be inferred that salicylate does not alter the volumes of intracellular and extracellular water. The addition of insulin is without effect on the total water content but leads to a small reduction in the thiosulphate space. Free glucose has an entirely extracellular distribution in the diaphragm in the presence or absence of insulin or salicylate,

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since in no instance does the glucose space exceed the thiosulphate space. In the same way D-xylose has a principally extracellular distribution in the absence of salicylate or insulin. When insulin or salicylate is present, however, D-xylose acquires a partially intracellular distribution and comes into equilibrium with about 40% of intracellular water (Table II).

Salicylate and Potassium Loss.—The presence of sodium salicylate *in vitro* leads to a greatly increased loss of potassium from the isolated rat diaphragm during incubation; neither sodium *p*-hydroxybenzoate nor insulin significantly affects the loss of potassium (Table I).

Salicylate and Incorporation of Amino-acids into Protein.—In the absence of salicylate, ^{14}C-labelled glycine, glutamic acid, and lysine are incorporated into protein of the isolated rat diaphragm. In the presence of salicylate ^{14}C incorporation into protein is very greatly reduced (Table III). On the other hand, when insulin is added *in vitro* incorporation of ^{14}C is substantially increased (Krahl, 1953; Manchester and Young, unpublished).

Discussion

These observations show that sodium salicylate increases glucose uptake and potassium loss by the isolated rat diaphragm and decreases incorporation into protein of ^{14}C-labelled glycine, lysine, and glutamic acid. On the other hand, sodium *p*-hydroxybenzoate does not stimulate glucose uptake (or potassium release), and this may be correlated with the fact that sodium *p*-hydroxybenzoate, unlike sodium *o*-hydroxybenzoate (salicylate), does not raise the B.M.R. *in vivo* (Cochran, 1954). The incorporation of amino-acids into protein and the maintenance of high intracellular potassium are processes known to be dependent upon the availability of high-energy phosphate, and the influence of salicylate upon these processes would be in keeping with the view that it interferes with the production of high-energy phosphate by oxidative mechanisms (uncouples oxidative phosphorylation). The diminution of incorporation of amino-acids into protein of the isolated rat diaphragm in the presence of salicylate is in accord with the observation that salicylate therapy promotes negative nitrogen balance in the intact animal. The fact that salicylate promotes glucose uptake by diaphragm in a bicarbonate-buffered medium would support the suggestion of Reid *et al.* (1957) that salicylate stimulates metabolism in peripheral tissues—that is, muscle.

This observation suggests that salicylate may reduce glycosuria and hyperglycaemia in diabetes by promoting the utilization of glucose by muscle. The finding by Reid *et al.* (1957) that salicylate raises the B.M.R. in diabetic as well as in non-diabetic subjects is in keeping with this idea. The limiting step in the utilization of glucose by muscle is thought to be the rate of entry of glucose into the muscle cell. Park, Bornstein and Post (1955), Park and Johnson (1955), and Levine and Goldstein (1955) believe that insulin accelerates the utilization of glucose by muscle by increasing the rate of entry of the sugar into the muscle cell. Park *et al.* (1955) have obtained evidence that insulin accelerates the uptake of glucose by the isolated rat diaphragm *in vitro* by this mechanism, and in keeping with this view is the observation that insulin increases the volume of distribution of the non-utilizable sugar D-xylose in the water of the isolated diaphragm (Kipnis and Cori, 1957). It is likely that the volume of distribution of glucose in the water of the isolated diaphragm is not increased by insulin under these

TABLE I.—*Influence of Sodium Salicylate* (5×10^{-3} M) *and of Insulin* (0.1 *unit/ml.*) *on Uptake of Glucose and Release of Potassium by the Isolated Rat Diaphragm in vitro*

Experiment No.	Addition to Medium	Glucose Uptake. Mean ± S.E. of Mean. mg. Glucose/g. of Wet Diaphragm/Hour of Incubation	Potassium Loss. Mean ± S.E. of Mean. μequiv. Potassium/g. of Wet Diaphragm/Hour of Incubation
	Bicarbonate-buffered Medium		
1a	No addition	2·5 ± 0·20 (14) } P < 0·001	8 ± 1·2 (14) } P < 0·001
1b	Sodium salicylate (5×10^{-3} M)	4·0 ± 0·28 (14)	31 ± 1·5 (14)
1c	Sodium *p*-hydroxybenzoate (5×10^{-3} M)	2·0 ± 0·21 (6) } P < 0·001	8 ± 0·9 (6) } P < 0·001
2a	No addition	2·3 ± 0·17 (6) } P < 0·001	8 ± 0·9 (6) } P < 0·05
2b	Insulin (0·1 unit/ml.)	9·1 ± 0·24 (6)	5 ± 0·9 (6)
	Phosphate-buffered Medium		
3a	No addition	3·2 ± 0·28 (6) } P < 0·001	17 ± 0·6 (6) } P < 0·001
3b	Sodium salicylate (5×10^{-3} M)	2·8 ± 0·13 (6)	42 ± 0·9 (6)

The value of P is given when the difference between means is significant. Number of observations is given in parentheses. Values derived from the incubation of hemidiaphragms.

TABLE II.—*Influence of Sodium Salicylate* (5×10^{-3} M) *and of Insulin* (0.1 *unit/ml.*) *on the Total Water Content and the Thiosulphate, Glucose, and Xylose Spaces of the Isolated Rat Diaphragm Incubated in a Bicarbonate-buffered Medium*

Experiment No.	Addition to Medium	Total Muscle Water μl. Water/100 mg. of Wet Diaphragm. Mean ± S.E. of Mean	Thiosulphate Space μl. Water/100 mg. of Wet Diaphragm. Mean ± S.E. of Mean	Glucose Space μl. Water/100 mg. of Wet Diaphragm. Mean ± S.E. of Mean	Xylose Space μl. Water/100 mg. of Wet Diaphragm. Mean ± S.E. of Mean	Glucose Uptake mg. Glucose Hour of Incubation
1a	No addition	74 ± 0·5 (6)	22 ± 1·3 (6)	17 ± 2·0 (6)	26 ± 0·6 (10) } P < 0·001	1·8 (6)
1b	Sodium salicylate (5×10^{-3} M)	75 ± 0·6 (6)	25 ± 1·3 (6)	18 ± 2·2 (6)	44 ± 3·0 (3)	3·8 (6)
2a	No addition	74 ± 0·9 (5)	21 ± 1·0 (5) } P < 0·05	16 ± 0·9 (5)	26 ± 0·6 (10) } P < 0·001	4·4 (5)
2b	Insulin (0·1 unit/ml.)	75 ± 0·5 (5)	17 ± 1·2 (5)	14 ± 1·4 (5)	48 ± 1·0 (4)	6·2 (5)

The value of P is given when the difference between means is significant. Number of observations is given in parentheses. The diaphragm preparation used in these experiments consisted of rib, vertebra, intercostal muscle, and the diaphragm with its attachments to these structures intact. Uptake of glucose under these conditions is not therefore by the diaphragm alone.

TABLE III.—*Influence of Sodium Salicylate* (5×10^{-3} M) *on Incorporation of ^{14}C from ^{14}C-labelled Glycine, Lysine, and Glutamic Acid into Protein of the Isolated Rat Diaphragm in vitro*

Addition to Medium	Incorporation into Protein, Mean ± S.E. of Mean, Counts/min./Protein Sample, in the Presence of		
	Glycine	Lysine	Glutamic Acid
No addition	448 ± 18 (4) } P < 0·001	1,399 ± 36 (4) } P < 0·001	193 ± 13 (4) } P < 0·01
Sodium salicylate (5×10^{-3} M)	204 ± 11 (4)	676 ± 26 (4)	92 ± 14 (4)

The value of P is given for the difference between means. Number of observations is given in parentheses.

conditions because the potential rate of intracellular utilization of glucose exceeds the rate of entry of glucose into the muscle cell (Park *et al.*, 1955). Salicylate, like insulin, increases glucose uptake, expands the xylose space, but does not alter the glucose space. We conclude, therefore, that the action of salicylate in increasing glucose uptake includes acceleration of the rate of entry of glucose into the muscle cell.

The observation that oxygen lack or substances such as cyanide, 2:4-dinitrophenol, and arsenite which inhibit oxidation or uncouple oxidative phosphorylation increase the uptake of glucose by the isolated rat diaphragm (Randle and Smith, 1957) has led to the suggestion that the entry of glucose into the muscle cells of this preparation is normally restrained by an active process (Randle and Smith, 1957). The present observations with salicylate lend support to this idea.

Although both insulin and salicylate increase the glucose uptake of isolated diaphragm their actions on the diaphragm with respect to potassium release and incorporation of amino-acids into protein differ greatly. Salicylate promotes loss of potassium from the muscle and diminishes the incorporation of amino-acids into protein, whereas insulin stimulates amino-acid incorporation and does not promote loss of potassium. Nevertheless both insulin and salicylate may accelerate glucose uptake by interfering with some restraint on glucose entry involving energy-rich phosphate ; salicylate, by restricting the oxidative production of energy-rich phosphate ; and insulin, not by interfering with the production of energy-rich phosphate, but perhaps by interfering specifically with the availability of energy-rich phosphate to a process concerned with the regulation of glucose entry. Such an action of insulin would neither be incompatible with its ability to stimulate incorporation of amino-acids into protein nor would it interfere with the maintenance of high intracellular potassium.

We attach more significance to the stimulating effect of salicylate on glucose uptake in bicarbonate-buffered medium than to the lack of this effect in a phosphate-buffered medium, because bicarbonate-buffered medium more closely resembles extracellular fluid in ionic composition. Furthermore, phosphate-buffered media are known to be unsuitable for incubation of tissues such as diaphragm which exhibit a high rate of glycolysis (Dixon, 1934), and phosphate-buffered media contain an abnormally high concentration of phosphate, an ion which in high concentration is itself capable of influencing glucose uptake (Villee, Deane, and Hastings, 1949).

Summary

Sodium salicylate, like insulin, increases the uptake of glucose by isolated rat diaphragm, and enables the non-utilizable sugar D-xylose to enter the muscle cells. Neither insulin nor sodium salicylate enables free glucose to accumulate within the cells of isolated diaphragm, presumably because the potential rate of glucose utilization with the cell exceeds the rate of entry of glucose into the cell. The effect of insulin on isolated diaphragm differs from that of salicylate in that salicylate promotes loss of potassium and diminishes incorporation of ^{14}C-labelled amino-acids into the protein, whereas insulin does not promote potassium loss and increases incorporation of labelled amino-acids into protein. The uptake of glucose into the cells of isolated diaphragm appears to be restrained by an active process, dependent upon the oxidative production of energy-rich phosphate. It is suggested that salicylate promotes uptake of glucose by inhibiting the production of energy-rich phosphate and that insulin promotes glucose uptake, more specifically, by limiting the availability of energy-rich phosphate to a process concerned with the regulation of the entry of glucose into the cell.

It is suggested that the antidiabetic action of salicylate results, at least in part, from its effect in increasing the utilization of glucose by muscle.

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EFFECT OF "NACTON" IN PATIENTS WITH DUODENAL ULCER

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One of the mainstays of treatment of patients with duodenal ulcer is the reduction of the acidity of the gastric contents. This is usually attempted by counteracting the acid physico-chemically with antacids. In addition, atropine and drugs with an atropine-like action have long been used to block excitation of the acid-secreting parietal cells. Generally these drugs have two disadvantages in that their action in reducing gastric secretion runs parallel with their side-effects, such as drying of the mouth and interference with visual accommodation, and their effect is capricious even in the hands of experienced workers (Kirsner and Palmer, 1953).

Investigation

The present paper describes the use of "nacton" (1-methyl-2-pyrrolidyl) methyl benzilate methyl methosulphate ; I.S. 499), a compound with an atropine-like action of long duration, which has given regular reduction of gastric secretion in patients with duodenal or gastric ulcer at dose levels that did not produce noticeable side-effects. The chemical (Doyle *et al.*, 1958) and pharmacological (Acred *et al.*, 1957) details and the results of a preliminary study in man (Douthwaite *et al.*, 1957) have been published.

Test-meal Method.—The technique (Hunt, 1954) involves washing out the stomach of fasting patients and giving a 750-ml. test meal containing 50 g. of glucose per litre and a dye which is not absorbed from the stomach. After 30 minutes the gastric contents are recovered, the usual volume being about 300 to 500 ml. when the completeness of the recovery has been checked by washing out the stomach. From the amount and composition of the dye remaining in the gastric contents the volume of the gastric contents which has passed into the duodenum may be assessed, together with the total amounts of acid, chloride, and pepsin secreted. It is then possible to describe the gastric secretion of acid in terms of millilitres of 0.16N hydrochloric acid, the concentration at which it is supposedly produced by the parietal cells (Fisher and Hunt, 1950).

Regulation of Dosage.—The method of regulation of the dosage of nacton varied during the trial, but the aim was to arrive at the maximum not giving side-effects. The first three patients were given the drug initially at eight-hourly intervals. When a change was made to six-hourly doses the incidence of side-effects appeared to be less, presumably because each dose was smaller, and this interval was maintained for all the other patients. The starting dose was usually 8–10 mg. a day, and this was increased at intervals by 4 mg. a day. When the patient became aware of definite side-effects the dosage was always reduced, usually by 4 mg. a day. With less definite side-effects—for example, a little dryness of the mouth in the morning—the dosage was not increased as it would have been had the patient not reported this symptom. These slight effects decreased in a day or two, and the dose was usually raised subsequently. An increased tolerance to the drug developed in some patients, so that the occurrence of a side-effect with a certain dosage during the first few days could not be taken to indicate that side-effects would necessarily reappear when the same dosage was reached 10 days later. A scheme of dosage for clinical use is suggested below.

The Patients.—Twenty-three male patients with a diagnosis of duodenal ulcer and two with gastric ulcer were studied while they were in hospital. In none of them was there any history of recent haemorrhage. Their mean age was 42 years, with a range from 21 to 66, five being over 60. The patients were in no sense specially selected for the trial, but were representative of a group which does not respond satisfactorily to treatment at home. Four patients were transferred for surgical treatment, three because of pyloric stenosis (7, 8, and 16), and a fourth (3) because of a history of many recurrences. In four other patients the prognosis was thought to be poor, but because they responded well to nacton it seemed advisable to reserve surgical treatment for the future.

To judge from their remarks and their co-operation as out-patients most of the patients found the inconvenience of the test meals balanced by the individual attention they received.

Procedure.—After the co-operation of the patient had been enlisted by explaining to him the purpose of the trial he was given a test meal. He next received placebo tablets at six-hourly intervals for three or four days and his gastric function was retested. From then onwards nacton was given at six-hourly intervals and gastric function was studied from time to time. On some days the test meal was given at 8 a.m. after the drug had been taken at 6 a.m.; on other occasions the morning dose was omitted and the test meal given at 8 a.m. Each patient, except three at New Cross General Hospital, was visited at least once every day by one of us and asked about side-effects and general well-being. The ordinary therapeutic regime as ordered by each physician was continued unchanged throughout the study of the patients except that those receiving belladonna were not given it within six hours of the tests. Some days before the patient was due for discharge nacton was withheld while he was given further test meals. When it became apparent that the drug could be used with safety the last 14 patients in the series were discharged with a supply to take at home. Their progress was checked periodically by tests made two hours after taking the drug.

Results

The account which follows is based on the results of 321 test-meal studies of 25 in-patients, the average period of observation of each in-patient being 30 days. Thirty-six studies of the gastric function of the last 14 of these patients were made during the early months after their discharge.

Patients in Hospital

Fig. 1 is a summary of the reductions of secretion of acid obtained without side-effects following six-hourly doses of

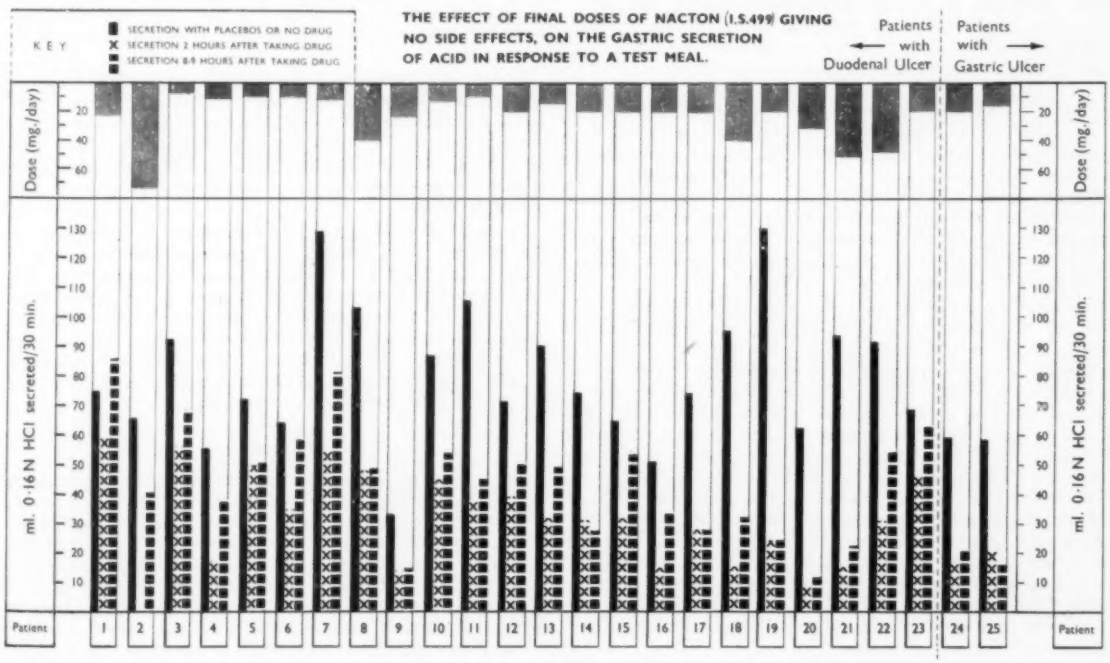
THE EFFECT OF FINAL DOSES OF NACTON (I.S.499) GIVING NO SIDE EFFECTS, ON THE GASTRIC SECRETION OF ACID IN RESPONSE TO A TEST MEAL.
K E Y
SECRETION WITH PLACEBOS OR NO DRUG
SECRETION 2 HOURS AFTER TAKING DRUG
SECRETION 8-9 HOURS AFTER TAKING DRUG
Patients with Duodenal Ulcer
Patients with Gastric Ulcer
Dose (mg./day)
ml. 0·16 N HCl secreted/30 min.
Patient

FIG. 1

nacton. The order is that in which the patients presented themselves. For each patient the height of the first column represents the volume of 0.16N HCl secreted in 30 minutes in response to the test meal when he was receiving placebo tablets or no tablets soon after admission. This value served as the control for the subsequent results. The second column represents the volume of the 0.16N HCl secreted in response to the test meal two hours after taking the drug, and the third column that secreted eight to nine hours after taking the drug. Each of these two values is the mean of two or more results obtained shortly before discharge. The dosage of nacton for each patient at this time is shown above his data.

In the first 10 patients with duodenal ulcer the mean gastric secretion of acid two hours after the dose was reduced to 52% of the uninhibited secretion in the control experiments, and eight to nine hours after the dose to 70% of the control. For the second 10 patients with duodenal ulcer the mean response two hours after the dose was 34% of the control, and eight to nine hours after the dose it was 47%. The improvement in the results with the second 10 patients was probably the result of our excessive caution in using the drug in the first 10. From the results for the second 10 patients with duodenal ulcer it can be seen that with six-hourly doses a continuous reduction of gastric secretion of acid to about 50% of the control in response to the test meal can be expected. In patients with marked hypersecretion the inhibition was often greater when expressed as a percentage of the control than in those with lower levels of secretion. Among those with duodenal ulcers the first patient (Case 1) and the last patient (Case 23) responded poorly to the drug. The two patients with gastric ulcer responded satisfactorily.

When the optimal dose was given the drug had little action in causing gastric retention. For the tests two hours after the drug the mean increase in the volume of the gastric contents 30 minutes after taking the meal was 50 ml. in the first 20 patients, an increase of 13%.

The mixed secretions of the cells of the gastric mucosa other than the parietal cells have been supposed to have a statistically constant composition (Fisher and Hunt,* 1950). These non-parietal secretions which originate from the whole area of the gastric mucosa are thought to contain bicarbonate ion at a concentration of 0.045N. Presumably these secretions have some protective function, and it is therefore worth recording that the mean output of this component in the first 20 patients with duodenal ulcer was found to be unaltered by full doses of nacton.

Patients Studied as Out-patients after In-patient Treatment

Detailed records of the studies of 14 of the last 15 patients are shown in Fig. 2. The dose of drug and the amounts of acid secreted in response to the test meals by in-patients and out-patients are shown plotted against time for each patient. The duration of in-patient treatment is shown in days; that for out-patients is given in weeks. So far nacton seems about as effective in reducing the secretion of acid in out-patients as it is for patients in hospital.

Relation Between Dose of Nacton and Inhibition of Gastric Secretion.—In the preliminary work (Douthwaite *et al.*, 1957) in connexion with nacton it was possible to establish a more or less regular relationship between the size of a single dose of the drug and the inhibition of the gastric secretion of acid. In the present studies with continuous dosage the relationship was not so clear, possibly because the effects of the drug were occasionally slow to develop. The record for Case 20 illustrates this: the drug had little action on gastric secretion during the first six days of treatment, although apparently it was absorbed, since there were urinary side-effects. Later, when dosage with the drug was restarted, a similar or slightly lower dose caused a progressive fall in the output of acid. In nine patients out of the last 14 the gastric secretion of acid after stopping treatment in hospital was found to be less than it was in the control studies before treatment.

Effect on Symptoms.—Doses of nacton which were effective in lowering gastric secretion did not immediately abolish pain, so that the drug presumably did not act as an anaesthetic. This is of some importance in that an increase in the size of the ulcer presumably would give rise to pain (Raftsky *et al.*, 1954).

Side-effects

The most frequent side-effect was dryness of the mouth. In a few patients there was difficulty in beginning to pass urine and in maintaining a vigorous stream. In Case 1 there was retention with a palpable bladder. However, when one dose of the drug was omitted this sign was abolished, and with a subsequent reduction in dosage it did not recur. Difficulty in micturition was usually accompanied by dryness of the mouth, which the patient counteracted by drinking. This further augmented the filling of the bladder and increased the discomfort. It was found best to allay the dryness of the mouth temporarily with mouth-washes.

The drug was given to three patients with pyloric stenosis (7, 8, 16), subsequently confirmed at operation, without producing any marked slowing in the gastric emptying of the test meal and without there being any ordinary food remaining in the stomach in the morning. In patient 5, who was found to have an enlarged prostate on rectal examination, the careful administration of nacton produced 30% inhibition of gastric secretion of acid without any urinary symptoms. With our present experience higher doses could have been tried.

Patients in hospital have reported interference with visual accommodation coming on after reading for some minutes. A raised heart rate has been the reason for reducing the dosage for only one in-patient (19), but in out-patients tachycardia has been noted in patients 12, 19, 24, and 17. It seems likely from the remarks of Nos. 12 and 19, who were able to record their pulse rates at home, that the maximal rate was reached about two hours after the morning dose but that similar rates were not reached after later doses. Since the out-patients are seen precisely at this time of day for their test meals it is possible that our routine has made this side-effect more likely than it will be in actual practice. Certainly the rates observed by Nos. 12 and 19 at home were 20–30 beats a minute less than those observed by us on the days of the tests. Should tachycardia occur it might be avoided by giving the dose after breakfast and after the midday meal, with the idea of slowing absorption of nacton.

Constipation when it occurred cleared up without reduction of the dosage of the drug in these 25 patients. It seems possible that the small amounts of magnesium which were present in the majority of the antacids which the patients were taking, together with the liquid paraffin often supplied in hospital, may have minimized the occurrence of this side-effect.

It must be emphasized that side-effects in hospital were for the most part deliberately produced, and were subsequently abolished by a small decrease in dosage. We observed in two patients that a dosage of the drug which produced no side-effects during continuous administration gave side-effects when it was restarted after an interruption of seven days. The reductions of gastric secretion recorded in Fig. 1 were observed in the absence of side-effects which we regard as an indication of overdosage.

Discussion

In 23 patients with duodenal ulceration under treatment in hospital it has been possible to reduce the gastric secretion of acid in response to test meals during the period between two hours and eight hours after giving doses of nacton carefully adjusted not to produce side-effects. For the second 10 patients with duodenal ulcer the secretion of acid was reduced to about half of the control value. Since in groups of patients with duodenal ulcer the gastric secretion of acid in response to test meals is about doubled (Hunt,

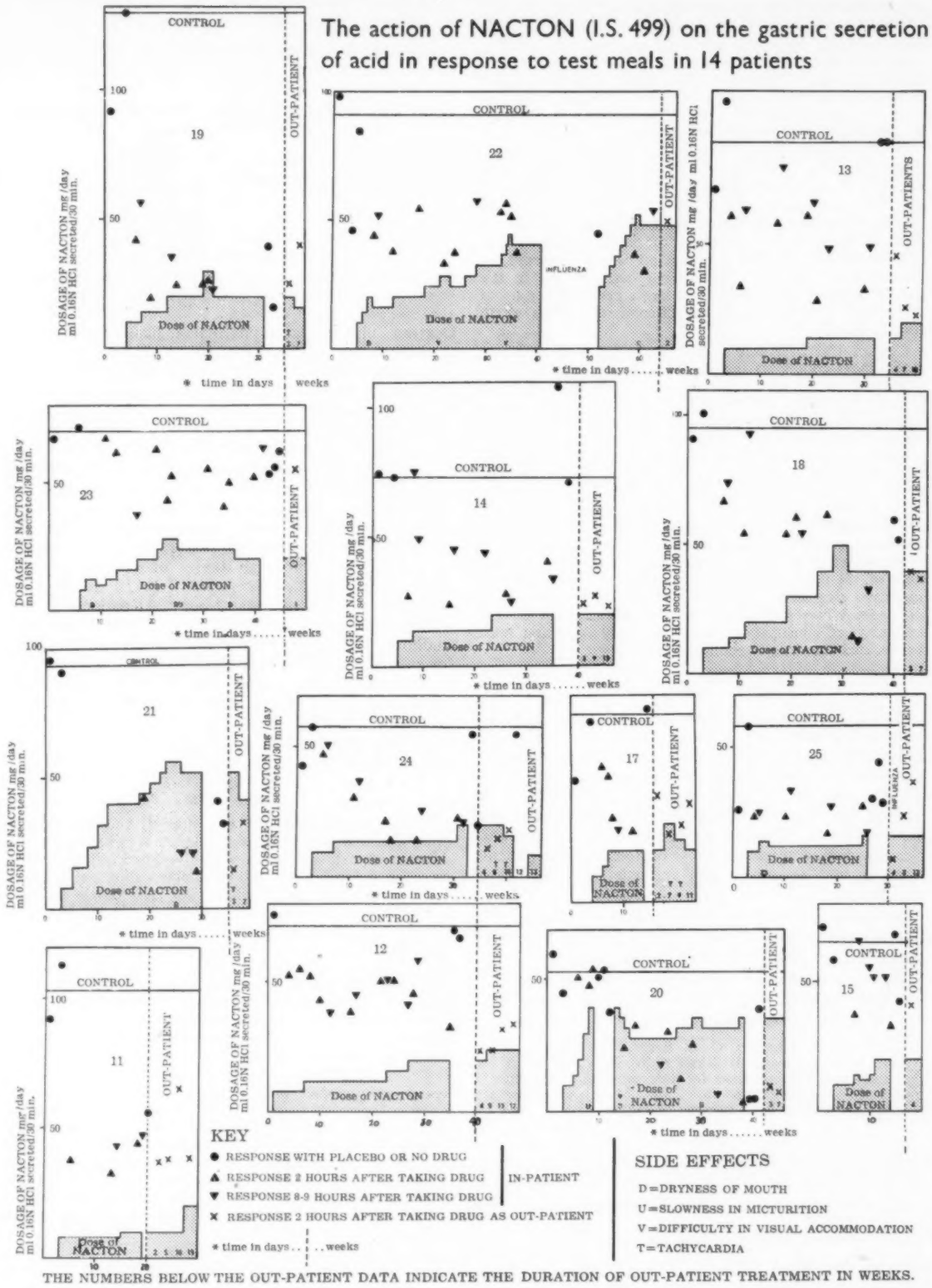
The action of NACTON (I.S. 499) on the gastric secretion of acid in response to test meals in 14 patients
CONTROL
OUT-PATIENT
Dose of NACTON
INFLUENZA
DOSAGE OF NACTON mg /day ml 0.16N HCl secreted/30 min.
* time in days ..... weeks
19
22
13
23
14
18
21
24
17
25
12
20
11
15
KEY
RESPONSE WITH PLACEBO OR NO DRUG
RESPONSE 2 HOURS AFTER TAKING DRUG
RESPONSE 8-9 HOURS AFTER TAKING DRUG
RESPONSE 2 HOURS AFTER TAKING DRUG AS OUT-PATIENT
IN-PATIENT
SIDE EFFECTS
D=DRYNESS OF MOUTH
U=SLOWNESS IN MICTURITION
V=DIFFICULTY IN VISUAL ACCOMMODATION
T=TACHYCARDIA
THE NUMBERS BELOW THE OUT-PATIENT DATA INDICATE THE DURATION OF OUT-PATIENT TREATMENT IN WEEKS.

FIG. 2

1957) as compared with that in healthy subjects, the drug may be said to correct this abnormality.

These results are probably relevant to the response to ordinary food, since the test meal used in this work is thought to stimulate gastric secretion by virtue of its volume (Macdonald and Spurrell, 1953; Hunt and Macdonald, 1954), a property necessarily common to all meals. Further work is required to decide whether nacton inhibits secretion in response to other modes of stimulation.

In view of the numbers of drugs which have been tried it is not surprising that another drug with atropine-like action has been found which will depress the gastric secretion of acid, but as compared with atropine the degree of specificity and the duration of its action are interesting. In our experience the maximal inhibition of gastric secretion was often obtained with doses of nacton which produced no noticeable side-effects. The finding that the fall in the gastric secretory response to test meals persisted for up to three days after the drug was discontinued seems worth further study.

Clinical Use of Nacton.—The study reported here was made under conditions remote from those under which inhibitors of gastric secretion can ordinarily be used, and it is clearly undesirable that the dose of nacton should have to be regulated by measurements of the gastric secretory response. However, our finding that full inhibition of gastric secretion of acid was often achieved by doses which produced no side-effects provides a means of regulating the dose by increasing it at four-day intervals from 2 mg. six-hourly to 3, 4, and 5 mg. six-hourly, and so on until side-effects are observed. The reduction of the dosage by one step abolished side-effects and usually gave satisfactory control of the secretion of acid. We observed in two patients that a dose of the drug adjusted to no side-effects on continuous use gave side-effects if it was restarted after seven days' omission. Where a short period of tachycardia, of urinary retention, of constipation, or of pupillary dilatation must be avoided the drug is contraindicated.

Summary

Twenty-three patients with duodenal ulcer and two with gastric ulcer were given six-hourly doses of nacton ((1-methyl-2-pyrrolidyl) methyl benzilate methyl methosulphate; I.S. 499), a drug with an atropine-like action of long duration, while they were in hospital. For each patient the final dose chosen was that which produced no side-effects. The changes in gastric secretion of acid were studied with test meals. Fourteen of these patients were treated as out-patients and studied with further test meals.

In the second 10 patients the gastric secretion of acid was reduced by half during a period between two hours and eight to nine hours after taking the drug.

Effective dosages of nacton produced little change in the rate of gastric emptying and no change in the mean output of gastric non-parietal secretions.

We are grateful to Drs. C. G. Baker, E. R. Boland, R. T. Grant, A. C. Hampson, R. Kauntze, W. N. Mann, and K. S. MacLean and their colleagues for their unfailing co-operation in this study of patients under their care. Messrs. C. L. Bencard Ltd. kindly gave us large amounts of nacton.

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ALOPECIA FOLLOWING TREATMENT WITH DEXTRAN SULPHATE AND OTHER ANTICOAGULANT DRUGS

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Dextran sulphate has a pharmacological action similar to that of heparin (Ricketts, 1952; Walton, 1952). It differs from heparin in its more prolonged anticoagulant and greater cumulative effects (Ricketts *et al.*, 1953; Donzelot *et al.*, 1955; Jeavons *et al.*, 1956; Cohen and Tudhope, 1956). The commonest toxic effect of dextran sulphate is transient alopecia, which has been described in about 10% of cases (Donzelot *et al.*, 1955; Jeavons *et al.*, 1956), but the frequency of this complication has probably been underestimated, because it may not appear until several weeks after treatment has been stopped. Hjort and Stormorken (1957) have described 10 cases treated with high dosage of dextran sulphate in which loss of hair developed 8 to 10 weeks later. We previously reported that 3 out of 11 patients treated with dextran sulphate developed loss of hair (Cohen and Tudhope, 1956); when these patients were followed up for a longer period the incidence of alopecia was found to be much greater, and we now report the occurrence of this and other toxic effects in 27 patients treated with dextran sulphate. The incidence of alopecia was also studied in 60 patients treated with heparin and an anticoagulant of coumarin type.

Clinical Data

Three groups of patients were studied: those in the first group received dextran sulphate alone; in the second group dextran sulphate was given with a coumarin drug; and in the third group heparin and a coumarin drug were used.

Group 1: Dextran sulphate (total dose 90,000 or more units).—Dextran sulphate was given by repeated intravenous injection to 15 patients. The individual dose was kept constant at 5,000 units, and the frequency of injection was varied in order to maintain the clotting-time at more than twice the value before treatment. It was found that, whereas injections were required eight-hourly during the first 24 hours, 12-hourly dosage was sufficient after 24 to 48 hours, and after 5 to 11 days of continuous treatment one injection every 24 hours was sufficient (Cohen and Tudhope, 1956).

Group 2: Dextran sulphate (total dose less than 40,000 units) with an oral anticoagulant.—Dextran sulphate was given concurrently with ethylbiscoumacetate or phenindione to 12 patients, 5,000 units being injected intravenously eight-hourly for 24 to 48 hours. Treatment was then continued with the oral anticoagulant, the dose of which was regulated to maintain the one-stage prothrombin time two to two and a half times the normal control. The average daily dose of ethylbiscoumacetate was 442 mg.; of phenindione it was 100 mg.

Group 3: Heparin and oral anticoagulant.—Heparin was given with an oral anticoagulant to 60 patients, in whom acute myocardial infarction was diagnosed in 46, pulmonary embolism in 12, and thrombosis of the leg veins in two. In

35 cases heparin was given by intravenous injections of 5,000–15,000 units at intervals of six to eight hours. The total amount of heparin injected is shown in Fig. 1. Administration of ethylbiscoumacetate (18 cases) or phenindione (17 cases) was started concurrently with the heparin, and was continued for 21 to 28 days in most cases. In 25 cases two intramuscular injections of 20,000 units of heparin were given at an interval of 12 hours; phenindione was started simultaneously and was continued for 21 to 28 days. The average daily dose of ethylbiscoumacetate in this group of cases was 660 mg.; of phenindione it was 110 mg.

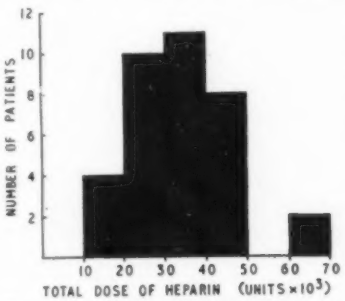

FIG. 1.—Total dose of heparin given by intravenous injection to 35 patients treated with heparin and an oral anticoagulant.

Patients in all groups were examined at least once, three to 12 months after the course of anticoagulant treatment, and most were seen on several occasions during that period. Each patient was specifically questioned about changes in the hair. In a few cases treated with dextran sulphate, alopecia occurred as long as two months after stopping treatment; therefore only patients who could be followed up for at least three months after treatment were included in this study.

Results

The occurrence of alopecia and other toxic effects in patients treated with dextran sulphate is shown in Tables I and II.

Dextran Sulphate—Total Dose at Least 90,000 Units

Alopecia.—Fifteen patients received 90,000 or more units of dextran sulphate, and eight of these developed severe alopecia, amounting to an almost complete loss of scalp hair in six; in addition, loss of pubic, axillary, and facial hair occurred in three patients. Three of those who suffered severe loss of scalp hair were women, one of whom had complete loss of axillary and pubic hair and partial loss of eyebrows. Two male patients reported that they had to shave much less often than normally for a few weeks. The loss of hair was diffuse, affecting the whole scalp, and was unassociated with any apparent change in the scalp itself; it was first noticed three to eight weeks after stopping treatment. Regrowth of hair was obvious after a further four to twelve weeks, and in all cases the hair eventually returned to normal. In one other patient a small occipital bald patch was noticed for the first time 10 days after starting treatment with dextran sulphate. This area of baldness remain unchanged during the following year. In this patient the type of alopecia was different, and it appeared much earlier in the course of treatment than in the other cases, so it is doubtful whether it was related to the dextran sulphate therapy.

Changes in Nails.—In three patients who developed severe alopecia, marked changes in the finger-nails occurred two to three months after dextran sulphate therapy, the nails becoming brittle and transversely ridged. In two of these patients all finger-nails split transversely, the distal parts of the nails being shed. In a fourth patient who did not develop any alopecia, transverse ridging of all finger-nails was noticed six weeks after stopping treatment. In all cases the nails eventually regrew normally.

Diarrhoea.—Severe diarrhoea with the passage of blood in the stools occurred in two patients after treatment with dextran sulphate for 14 days. The total doses were 140,000 and 185,000 units; in fact, these two patients received a larger average daily dose than any other patients in this series. Sigmoidoscopic examination showed that the mucosa was diffusely congested, but neither ulceration nor other local lesion was seen. The diarrhoea persisted for seven days after stopping dextran sulphate. Two other patients had mild diarrhoea, without blood in the stools, after receiving total doses of 90,000 and 130,000 units of dextran sulphate. There was no apparent correlation between the occurrence of diarrhoea and of alopecia. Of the eight patients with severe loss of hair, only two had diarrhoea, which was mild in both cases.

Reduction in Platelets.—Repeated platelet counts were carried out in four patients during treatment with dextran sulphate. A substantial fall in the platelet count occurred

TABLE I.—*Incidence of Alopecia and Other Toxic Effects after Treatment with Dextran Sulphate (Total Dose 90,000 Units or More). Recent Myocardial Infarction was Diagnosed in All Patients Except Nos. 7 and 14, who had Severe and Persistent Angina Following a Previous Myocardial Infarction*

Case No.	Sex	Age (Yrs.)	Duration of Treatment (Days)	Total Dose of Dextran Sulphate (Units)	Loss of Hair	Changes in Nails	Other Toxic Effects
1	M	53	25	205,000	+	+	—
2	M	45	30	195,000	+	—	—
3	M	63	14	185,000	—	—	Diarrhoea; blood in stools
4	M	53	21	185,000	+	+	—
5	M	58	23	180,000	—	—	—
6	M	65	22	160,000	—	+	—
7	M	60	24	160,000	+	+	—
8	M	52	14	140,000	(+)	—	Diarrhoea; blood in stools; sore tongue; anorexia
9	M	56	18	140,000	—	—	—
10	F	62	22	135,000	+	—	Anorexia
11	F	66	19	130,000	—	—	—
12	F	63	20	130,000	+	—	Diarrhoea
13	M	57	14	125,000	—	—	—
14	M	45	19	125,000	+	—	—
15	F	71	11	90,000	+	—	Diarrhoea

In Case 8 the loss of hair was slight (see text).

TABLE II.—*Incidence of Alopecia after Treatment with Dextran Sulphate and an Oral Anticoagulant Drug*

Case No.	Sex	Age (Yrs.)	Diagnosis	Total Dose of Dextran Sulphate (Units)	Oral Anticoagulant	Duration of Anticoagulant Therapy (Days)	Alopecia	Remarks
16	M	58	Persistent angina	30,000	Ethyl biscoumacetate	17	+	—
17	M	62	Thrombosis of I.V.C.	30,000	,,	21	—	—
18	M	42	Myocardial infarction	25,000	,,	2	—	Haematemesis after 2 days. Previous history of dyspepsia
19	M	52	,, ,,	25,000	,,	20	—	Treated with dextran sulphate again 9 months later (Case 8, Table I)
20	M	50	,, ,,	25,000	Phenindione	24	—	—
21	M	42	Venous thrombosis of leg and pulmonary embolism	20,000	,,	18	+	—
22	M	53	Myocardial infarction	15,000	,,	28	—	—
23	M	60	,, ,,	15,000	,,	28	—	—
24	M	50	,, ,,	15,000	,,	29	—	—
25	M	56	,, ,,	15,000	,,	23	—	—
26	F	45	Pulmonary embolism	15,000	,,	10	—	—
27	M	55	Venous thrombosis of leg	15,000	,,	11	—	Bronchial carcinoma

in two of these patients, both of whom subsequently developed a severe degree of alopecia (Figs. 2 and 3). In the other two, of whom one suffered alopecia and the other developed changes in the nails without alopecia, no significant change occurred in the platelet count during treatment with dextran sulphate.

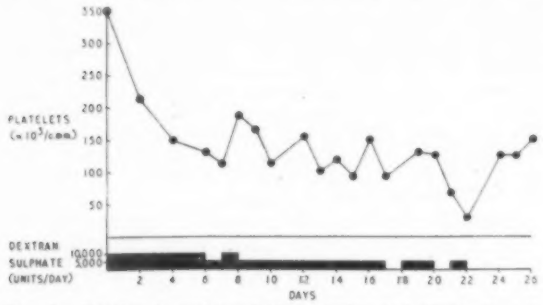

FIG. 2.—Platelets in peripheral blood during and after treatment with dextran sulphate in a case of myocardial infarction. Severe alopecia developed four weeks after stopping administration of dextran sulphate.

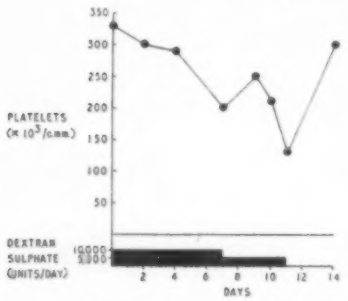

FIG. 3.—Platelets in peripheral blood during and after treatment with dextran sulphate, which was stopped after 11 days because of the development of diarrhoea. Severe alopecia occurred three weeks after the end of treatment.

Single platelet counts were performed 3 to 15 days after starting treatment in four other patients, two of whom subsequently developed alopecia. These platelet counts were all in the range of 200,000–350,000, so that thrombocytopenia was not detected during therapy.

Dextran Sulphate—Total Dose Less Than 40,000 Units

In the second group of 12 patients who received less than 40,000 units of dextran sulphate in addition to ethylbiscoumacetate or phenindione, two reported a mild loss of hair one to two months after the end of anticoagulant treatment. In both cases the hair loss was very mild and quite unlike the severe loss which occurred in patients of the first group.

Heparin and Oral Anticoagulant

Of the 60 patients treated with heparin and a coumarin drug, three reported loss of hair (Table III) and Case III had an extensive erythematous eruption while in hospital, suspected, but not proved, to be due to sensitization to phenindione. The loss of hair in this case occurred three weeks after discharge from hospital when the rash had entirely disappeared.

Discussion

Alopecia has been reported as a toxic effect of several heparin-like anticoagulants. Hirschboeck *et al.* (1954) found this complication in 19% of 68 patients treated with "treburon"; the loss of hair persisted for three to five months and involved mainly the scalp; axillary and pubic hair and eyebrows also became scanty in several patients. May (1951) reported transient alopecia in 70% of patients treated with "thrombocid." Dextran sulphate treatment has been previously reported to be followed by alopecia in 10% of cases (Donzelot *et al.*, 1955; Jeavons *et al.*, 1956). Using a higher dosage than most other workers, Hjort and Stormorken (1957) found that all 10 patients who received 20,000 units of dextran sulphate daily for 10 days suffered loss of hair. We observed severe alopecia in 8 out of 15 patients who had been followed up for at least three months after receiving 90,000 or more units of dextran sulphate; in three of these cases alopecia was not apparent until two months after the end of treatment. The lower incidence of alopecia reported by some other workers with dextran sulphate may be due partly to smaller dosage (Donzelot *et al.*, 1955) and partly to inadequate follow-up, as it was not at first realized that a latent period of two months might elapse between treatment and loss of hair (Jeavons *et al.*, 1956). The incidence of alopecia is much less when a smaller dose of dextran sulphate is given, and in the present study only 2 out of 12 patients receiving less than 40,000 units of dextran sulphate, along with a coumarin anticoagulant, developed mild alopecia. With treburon, Hirschboeck *et al.* (1954) found that the occurrence of alopecia appeared to bear no relationship to the total dose.

We also report diarrhoea in 4 out of 15 patients receiving at least 90,000 units of dextran sulphate; in two of these cases the diarrhoea was severe and was associated with the passage of blood in the stools. This has also been reported with treburon (Hirschboeck *et al.*, 1954).

Brittle and ridged finger-nails were observed in four patients treated with dextran sulphate, in three of whom severe alopecia also occurred. The only previous reports of such changes in the nails with heparin-like substances have been of one patient treated with treburon (Hirschboeck *et al.*, 1954) and another with dextran sulphate (Hjort and Stormorken, 1957).

There have been several accounts of alopecia occurring as a toxic effect of heparin, but estimates of the frequency of this complication have varied greatly. Merz (1950) reported alopecia in 54–66% of obstetrical and gynaecological cases treated with heparin; it affected the whole scalp but recovered spontaneously. Fischer *et al.* (1953) found that some degree of loss of hair occurred in 70% of patients who had been treated with a combination of heparin and a coumarin anticoagulant. They also reported that 30–40% of patients treated with coumarin drugs alone develop some loss of hair, and this appears to be the only report of alopecia occurring after coumarin drugs alone. Engelberg *et al.* (1956) gave 200 mg. of heparin subcutaneously twice weekly to 105 patients for 2 to 27 months and reported four cases of mild or moderate alopecia. Single cases of alopecia following heparin therapy have been reported by Plancherel (1952) and by Hirschboeck *et al.* (1954). On the other hand, various reviews of the actions

TABLE III.—*Details of Three Patients in whom Loss of Hair Occurred after Treatment with Heparin and Ethylbiscoumacetate or Phenindione*

Case No.	Sex	Age (Yrs.)	Diagnosis	Total Dose of Anticoagulant Drugs	Duration of Anticoagulant Treatment (Days)	Time from End of Treatment to Appearance of Alopecia (Weeks)	Type of Alopecia
I	M	42	Myocardial infarction	Heparin—20,000 units i.v. Ethylbiscoumacetate—8,000 mg.	21	3	Scalp only; mild diffuse loss of hair
II	M	47	,,	Heparin—30,000 units i.v. Ethylbiscoumacetate—8,350 mg.	23	4	Scalp only; marked diffuse loss of hair
III	M	65	,,	Heparin—40,000 units i.v. Phenindione—1,200 mg.	21	9	,, ,, ,,

and uses of heparin have contained no reference to the occurrence of alopecia (Jorpes, 1946, 1950; Best and Jaques, 1948; Duff *et al.*, 1951).

Wright (1953), in discussing the uses and toxic effects of anticoagulant drugs, did not mention alopecia with heparin, although stating that this complication occurs with the other sulphated polysaccharide anticoagulants, treburon and "paritol." De Takats (1953) stated that he had treated many hundreds of patients with heparin without observing alopecia, and suggested an impurity in some preparations as the cause. The latent period between treatment and obvious effect on hair, which is one to four months (Merz, 1950), may explain why some cases of alopecia have not been observed, but this is not likely to account for the big discrepancies in its reported incidence. It is more likely that a large total dose given during a period of a few weeks is the most important factor in the production of alopecia by heparin, as we have shown to be the case with dextran sulphate. We found that only 3 out of 60 patients treated with heparin and a coumarin-like anticoagulant developed alopecia. Merz (1950), in reporting that over 50% of patients treated with heparin developed alopecia, was referring mainly to treatment with heparin alone for several days or weeks, so that the total dosage was much greater than in the usual current practice of giving heparin for only 24 to 48 hours. It is probable that the incidence of alopecia with dextran sulphate is not any greater than with heparin in the same total dose.

Heparin causes a transient but profound decrease in circulating platelets when injected intravenously in dogs (Copley and Robb, 1941; Fidlar and Jaques, 1948), but not in man (Quick *et al.*, 1948). Plancherel (1952), however, found a reduction in platelets in 13 out of 30 cases during treatment with a long-acting preparation of heparin. Walton (1953) suggested that where heparin had been shown to cause reduction in platelets in man the effect was due to contamination with chondroitin sulphate of larger molecular weight than heparin. Several synthetic sulphated polysaccharides cause agglutination of platelets *in vitro* (Astrup, 1953) and when injected intravenously in rabbits (Piper, 1945). Dextran sulphate, of molecular weight about 7,500, does not cause agglutination of platelets following a single intravenous injection in rabbits (Walton, 1954; Astrup *et al.*, 1955). Hjort and Stormorken (1957) found that a significant decrease in circulating platelets occurred in man during treatment with repeated injections of dextran sulphate. We found that in two out of four patients in whom repeated counts of platelets were made during treatment with dextran sulphate there was a reduction in platelets occurring over several days, in one case reaching 30,000/c.mm. after 22 days. This is unlike the sudden and transient fall in platelet count occurring in animals after injection of some sulphated polysaccharides. The mechanism of platelet depression in these two patients is so far unexplained, but it is of interest that both subsequently developed severe alopecia.

The high incidence of alopecia, the occurrence of severe diarrhoea in some cases, and the possibility of a profound reduction in platelets in at least a few cases make treatment with dextran sulphate in high dosage clearly undesirable. In spite of the advantage of good control of clotting-time with infrequent injections, it is now clear that, when given in a total dose of more than 90,000 units, toxicity occurs too often. We have not observed any toxic effects when the total dose is less than 40,000 units; thus 5,000 units of dextran sulphate intravenously eight-hourly for 24 to 48 hours appears suitable as an alternative to heparin to cover the period until an oral anticoagulant becomes effective.

The mechanism by which dextran sulphate produces its effect on hair growth is unknown, but it possibly interferes with the metabolism of the naturally occurring sulphated polysaccharides or the sulphur-containing amino-acids. This problem is being investigated.

It is of great interest that the toxic effects of dextran sulphate—namely, alopecia, diarrhoea, thrombocytopenia, anorexia—are similar to some of the effects of whole-body irradiation, and of nitrogen mustards, colchicine, and other antimitotic substances, as well as of the folic acid antagonists. It has been shown that heparin itself has an antimitotic action (Heilbrunn and Wilson, 1949), and it is probable that dextran sulphate is similar in this respect. Furthermore, a heparin-like substance may be present in the blood following therapeutic doses of nitrogen mustards in man (Jacobson *et al.*, 1948) and after whole-body irradiation in animals (Allen and Jacobson, 1947). It has been suggested that some of the effects of irradiation may be due to the liberation into the blood of a toxic substance. Indeed, Van Dyke and Huff (1949) showed that irradiation of one member of a pair of parabiotically united rats produced loss of hair in both members of the pair. The production of alopecia by dextran sulphate may be only one aspect of a more general and fundamental action of the drug.

Summary

Severe alopecia occurred in 8 out of 15 patients treated with the anticoagulant drug dextran sulphate when the total dose was 90,000 or more units. Less than 40,000 units of dextran sulphate given with a coumarin anticoagulant produced mild loss of hair in 2 out of 12 patients.

Of 60 patients treated with heparin and a coumarin anticoagulant, three reported mild or moderate loss of hair following therapy.

Diarrhoea and depression of the platelet count were also noted in a few patients receiving a large total dose of dextran sulphate.

Previous reports of alopecia following anticoagulant treatment are reviewed.

All the patients treated with dextran sulphate were under the care of Professor G. M. Wilson, to whom we are grateful for advice and criticism. We thank Dr. T. E. Gumpert, Dr. A. W. D. Leishman, and Dr. R. S. Weetch for permission to study patients who had been under their care; Dr. E. K. Blackburn and the staff of the department of haematology, Royal Infirmary, Sheffield, who performed the platelet counts; Dr. K. Hardy, medical superintendent, Wharncliffe Hospital, for assistance in tracing case records; and Glaxo Laboratories Ltd., who supplied the dextran sulphate.

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OUT-PATIENT GYNAECOLOGY

BY

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Patients are referred to a gynaecologist for many reasons. Usually they have symptoms at least partly associated with the genital tract. Often these symptoms, however, are not entirely accounted for by the presence of a physical abnormality.

This report is based on a combined study of a small random series of women referred to a gynaecology clinic. The bodily and the mental state of these patients have been carefully analysed, and from this an attempt has been made to assess the relationship between physical and emotional factors in the development of symptoms.

Method

The study was carried out in the out-patient department of the Obstetric Hospital, University College Hospital, from June 1, 1953, to May 31, 1954. A sample was drawn from the total number of patients applying for consultations at the hospital during the year. The reception staff took two patients from those telephoning for an appointment in each week of the year, except for holidays, and entered their names for the clinic held on Wednesday afternoons. At the time of entry the receptionist knew nothing of the patient except her name, and the only selective factor here was the patient's willingness to attend on a Wednesday afternoon.

At the clinic, the two observers sat in adjoining rooms; each saw one patient, and the patients were then changed over. It was explained to each of them that she would see two doctors, one of whom would perform a gynaecological examination. The patients accepted this arrangement without dismay. Only one of the whole series inquired into the reason for it. One of us (N. M.) took a history and made a physical examination. The other made an appraisal of the woman's medical and psychiatric state. The two examinations were made separately and there was no consultation until both were concluded. Most patients were seen more than once by each observer, and some attended subsequently for gynaecological or psychiatric care. Observations made at these later attendances were used to confirm or refute the diagnostic impressions of the first interview.

In our view, the series as a whole may reasonably be regarded as representative of the "out-patient population" of this clinic.

Characteristics of the Test Series

The total number of cases seen was 64. The age range was 16 to 57, with a mean age of 33. The period of observation ranged from a single interview to 13 months. Eighteen patients attended only once. The mean period of observation in the rest was 6.4 months. Four patients came to inquire whether or not they were pregnant or to arrange antenatal care. The series under consideration therefore comprises 60 patients. The list of leading symptoms is given below, the leading symptom being here defined as the one first mentioned by the patient.

Pain, apart from period pain	.. ..	22	
Discharge	.. ..	14	
Menorrhagia	.. ..	7	
Period pain	.. ..	5	
Amenorrhoea	.. ..	2	
Irregular periods	..	2	
Morning sickness	..	1	
Fatigue	.. .. ..	1	
Frigidity	.. ..	1	
Headache	.. ..	2	
Bad nerves	.. ..	1	
Depression	.. ..	2	

When a detailed history had been taken and a full clinical appraisal made it was found that only seven of these 60 patients complained of one symptom only. In the remaining 53 the clinical picture included two or more symptoms. The largest number was in Case 1 ("Discharge, irregular periods, loss of weight, fatigue, breasts smaller, funny heads, go hot and cold, can't sleep, don't eat").

Thirty-six patients complained of one or more of the following symptoms: fatigue, tension, depression, irritability, faintness, lack of energy, being run down, shakiness, insomnia, malaise, giddiness, bad dreams, going hot and cold, and other symptoms indicative of a state of emotional tension.

Pain

Twenty-two patients gave pain (apart from period pain) as a leading symptom. Of the other 38, 12 described pain as one part of their complaint. Period pain is dealt with separately. Pain of other types formed part of the clinical picture in 34 patients, or more than half of the whole series. The most common site of pain was the abdomen (11), and the next in order were back (7), head (6), shoulders (3), groin (2), neck (2), chest (1), buttocks (1), and armpits (1). In only three cases was the pain as described by the patient fully accounted for by the demonstration of a physical disorder. These were: (1) an inevitable abortion, (2) uterine enlargement due to fibromyomata, and (3) endometriosis of the ovary. In a few cases there was some minor disorder, such as a cervical erosion or laceration. However, this could not be regarded as of such an extent as to account fully for the patient's symptoms. Therefore, in the majority of patients complaining of pain no physical abnormality was discovered, but in nearly every instance emotional tension was clearly evident. The following case illustrates this picture.

Case 3.—A woman of 21 complained of a dragging pain in the right iliac fossa, a rash "all over the body," and period pain. Her home, in Liverpool, was an unhappy one: "I was always fed-up and depressed. Mother was too strict." She ran away at 20, and came to London. The year previously she had married a coloured man after an acquaintance of two weeks. "Life is very bad. I want to go home. Can't get on with my husband. He doesn't like my girl friends. Beats me up if I try to go." After a fight with him she purposely drank part of a bottle of "dettol." She was taken to hospital and given a stomach wash-out. The abdominal pain began after drinking the dettol, and lasted about 10 days. The psychiatric diagnosis here was depression in an immature, dull, and backward person, and the emotional component in the illness was assessed at 100%.

In many of these patients the character of the pain, its time relation and site, and its response to therapy were consistent with a diagnosis of tension pain (O'Neill, 1955). An underlying fear of cancer, in our experience, was a common association in many women with pain of "non-organic" distribution.

The pain sites in these patients differ from those in patients with tension pain who attend a department of physical medicine, in that there is a greater frequency of pain in the abdomen and lower part of the body, and less in the neck, shoulders, and back. In other respects, however, the two groups resemble each other closely. Patients with tension pain who find their way to physical medicine departments are mostly women, and in them too the onset and course of the illness are related to stress. A higher incidence of abdominal pain in our series is to be expected, since it is the pain in this region which determines the woman's referral to a gynaecological clinic.

Vaginal Discharge

Fourteen patients gave vaginal discharge as the leading symptom, while seven others mentioned discharge among their other complaints. There was a clear-cut physical explanation in only four of these patients. Two had acute trichomonal vaginitis, one a cervical polyp, and another cervicitis. In the other 10 no definite physical lesion was identified. On the other hand, all these patients had a significant degree of emotional tension. It is well established that vasomotor rhinitis is often associated with emotional tension, and it is not impossible that a similar association may be found in regard to the cervix.

Case 1.—A woman of 23 complained of a persistent vaginal discharge. She had never succeeded in bearing a live child, in spite of four pregnancies. Naturally she was extremely apprehensive about the prospect of another pregnancy, and in addition she was concerned over her physical state, complaining that she was losing weight and that her breasts were shrinking. In fact, no physical abnormality was demonstrated. She showed the signs of an acute anxiety state with considerable depression. She attended the clinic regularly and was seen by one of us (D. O'N.) on six occasions. Here she talked freely of her doubts and fears and was given reassurance. From her story it seemed possible that there might have been a stress factor associated with her repeated miscarriages, and this aspect of the disorder was fully discussed. At her last visit she felt much better and the discharge, in company with all her other symptoms, had dwindled considerably.

Menorrhagia

Menorrhagia is a relatively common gynaecological symptom, and can arise from several organic disorders, such as fibromyomata, subinvolution, adenomyosis, and certain disorders of the blood. Frequently, however, no physical cause is to be found. Blaikley (1949) called attention to the importance of menorrhagia of emotional origin.

In our series, seven patients gave menorrhagia as a leading symptom. All of these had a uterine curettage performed—three in combination with a vaginal repair operation. Histological examination of the endometrium showed no gross abnormality. In five out of the seven the bleeding was one bodily component of a response to stress, the factors concerned being: Case 26, intense domestic friction; Case 27, bad housing; Case 28, fear of pregnancy (in this patient the menorrhagia cleared after an operation for sterilization); Case 47, fear of disorderly and violent tenants in the house; Case 15, fear of cancer.

Period Pain

Five patients gave pain at the period time as a leading symptom. In each case these were quite young women, and the pain was of the type usually referred to as primary spasmodic dysmenorrhoea. No organic abnormality was found in any of these cases. In three, however, there was an obvious stress factor, which was at least causing some intensification of the pain experienced.

Case 42.—A girl of 18 had come to London to escape from her parents and was conducting an affair with a married man, over which she felt a great deal of guilt. The periods had begun at 15. She had suffered some pain with the first period, and on three later occasions, but after her arrival in London she had severe pain with every period. "I vomit, and have to lie down. Must stop work. Feel miserable."

It is of course not our view that stress is the sole cause of period pain, but from our experience there seems to be no doubt that emotional tension can stimulate pain at the period in a woman who has not suffered it before, and can intensify period pain already present. Other symptoms, such as depression, malaise, or vomiting, can also make their first appearance at a time of stress. Pain at the period was also mentioned as one symptom by seven other patients, Cases 3, 29, 39, 41, 55, 59, and 62; all these patients were manifestly anxious or depressed, or both.

Other Symptoms

Amenorrhoea.—Two patients came to hospital because they developed secondary amenorrhoea.

Case 50.—A woman of 24 came for advice because she had had amenorrhoea ever since the birth of her second child. She was very worried about a further pregnancy, which she did not want. She had little appetite, felt listless, and was very depressed. She had occasional headaches of a migrainous type. She was examined, was reassured that she was not pregnant, and was sent for advice about contraception. Four weeks later menstruation began again.

Irregular Menstruation.—Two patients complained of irregular periods, and in both the symptom was associated with a manifest emotional disturbance.

Miscellaneous Ailments.—One patient attended for advice about morning sickness and was found to have a normal pregnancy. The remainder—one case each of fatigue, frigidity, and bad nerves, two cases of headache, and two of depression—were thought to be suffering from psychiatric rather than gynaecological disorders.

Assessment of Cases

As a result of the combined assessment of all the cases seen it was decided to divide them into four categories.

Group 1 (12 cases).—Patients in whom an organic abnormality appeared to explain all the symptoms.

Group 2 (6 cases).—Patients in whom an organic abnormality accounted for most of the symptoms, but in whom there appeared to be also an emotional factor.

Group 3 (18 cases).—Patients whose symptoms appeared to arise in the main from emotional tension, but who had a minor organic abnormality.

Group 4 (24 cases).—Patients whose entire illness was a stress disorder.

Comment

The outstanding conclusion from our survey is that emotional tension outweighed physical malfunction and disease as a cause of illness.

This conclusion is surprising, and not at first sight easy to accept, yet the clinical observations seem inescapable, and the case histories speak for themselves. We tried to guard against an over-estimation of the emotional factor by careful appraisal of the whole clinical picture, by following up each case so that first impressions could be checked, and by interviewing the patient's relatives, where this was possible. Another useful check was the effect on symptoms of the brief and simple kind of psychotherapy which could be carried out in an out-patient department. Twenty patients who attended for repeated interview for this purpose reported that they had gained much benefit, or were entirely relieved. We believe that the series reported here is a representative one, and that women suffering from physical concomitants of emotional tension do in fact form a large part of the out-patient attendance at a gynaecological clinic.

Summary

A combined surgical and psychiatric survey of a random series of 60 women attending an out-patient clinic for gynaecology is reported. The largest single group was that of women who gave pain as the leading symptom; of these 22 cases, only 3 were proved to have any significant gynaecological abnormality.

The conclusion of the survey is that emotional tension outweighs physical malfunction and disease as a cause of illness in women who attend a gynaecology clinic.

We are indebted to Professor W. C. W. Nixon for his constant help and encouragement in the preparation of this study.

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OSTEOARTHRITIS OF THE KNEE

TREATMENT BY LOCAL INJECTION OF SALICYLATE COMPOUNDS

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Many attempts have been made to relieve the symptoms of osteoarthritis by injection into the affected joints, and a wide variety of materials have been tried: König (1932) used iodized oil; Thomson (1933) used Pregl's solution of iodine with sodium bicarbonate and sodium chloride in a watery solution; Andernach and Löhr (1936) used pure liver injections. These were for the most part small series, and though the respective authors claimed encouraging results none of their methods has found general acceptance.

Waugh (1938) claimed that the synovial fluid in traumatic effusions and rheumatoid arthritis was more alkaline than normal tissue fluid, and reported uniform improvement in such cases from aspiration followed by the intra-articular injection of an acid solution of lactic acid and procaine at *p*H 5. Later, Waugh (1945) reported a series of 26 consecutive cases of monarticular osteoarthritis of the hip treated by injections of a lactic acid and procaine mixture at *p*H 5.8, in which over 50% followed up for more than two years were said to have obtained enough help to carry on their normal occupations.

Crowe (1944), accepting Waugh's *p*H findings, used a solution of acid sodium phosphate in isotonic saline, claiming that this had a more prolonged effect than lactic acid on the *p*H of the joint fluid. In 93 cases of osteoarthritis he claimed excellent results in about 20% and improvement in every one of the remainder. Mawson (1946), Heald and Martin (1947), and Paraf, Abaza, and Peretz (1949) all reported favourable results with Waugh's solution.

Other authors, however, were far more critical. Baker and Chayen (1948) compared the results after intra-articular injections of Waugh's solution with those produced by solutions of procaine in water, sodium phosphate solution in water at *p*H 7.6, and normal saline. The results were not significantly different and they concluded that the acid solution produced no benefit compared with those of physiological *p*H. Nicholson (1948) criticized Waugh's *p*H estimations, and Kron (1948) reported encouraging results from the intra-articular injection of an isotonic solution of sodium bicarbonate in 15 cases. Lawther (1949) produced equal results in osteoarthritic hips by intra-articular injections of lactic acid and procaine solution, or procaine hydrochloride solution alone.

Desmarais (1952) recorded detailed results in the treatment of 189 cases of osteoarthritis of the hip and knee. Three groups were injected respectively with alkaline procaine solution at *p*H 7.4, Waugh's lactic acid procaine solution at *p*H 5.4 and saline at *p*H 7.2; in the fourth group the affected joint was needled with no injection. The same procedure was repeated several times in each case. Some members in each group improved, but the differences between them were not statistically significant. The *p*H of the synovial fluid was investigated in 10 of the osteoarthritic knees before treatment, and in every case it was found to be normal. No large or lasting change in *p*H followed the lactic acid injections, and the author remarked that synovial fluid acts as a strong buffer.

Present Investigation

This investigation is based on the work of G. Laughton Scott. After seeing several arthritic patients who had derived benefit from repeated intra-articular injections of an oily preparation by a foreign physician who refused to divulge its formula, Scott started a protracted investigation of various oils, and later of other substances dissolved in oil. He concluded that none of the oils tried alone produced any benefit, but he found that the use of oil as solvent for other substances injected into joints prolonged their local action and reduced their rate of excretion. After trying many such substances he published (Scott, 1943) a series of 96 consecutive cases of osteoarthritis and other "rheumatic" disorders treated by local injection of 10% benzyl salicylate in oil, with 79% good results. The number of osteoarthritic cases was not specified. Scott continued to use benzyl salicylate in oil until his death, but modified the formula to that which has been used in the present investigation. Benzyl salicylate was evidently chosen because it is the most readily oil-soluble salt of salicylic acid. For intra-osseous injection Scott tried various watery salicylate solutions. The one used in our investigation was that favoured by him for this purpose in his later years.

Elkin (1945), using 10% benzyl salicylate solution in oil, recorded very encouraging results in a series of 25 patients with severe osteoarthritis of the hip- and knee-joints. Although the number is small, Elkin's figure of 80% improvement is similar to our own. Broadman (1954) in the United States wrote enthusiastically of the results in osteoarthritis and fibrositis, though he quoted no figures.

The cases here recorded received all their injections from K. A. R., who worked with Scott during his latter years and has continued to use his technique since his death. The assessment before and after treatment was conducted by M. M. S., who undertook the original investigation on behalf of the Dora Garrod Thomas Trust. This is a completely unselected series of cases; every new patient attending the orthopaedic out-patient department in whom osteoarthritis of one or both knees was diagnosed was referred for assessment and treatment. Of the 57 patients who were referred in this way, four failed to attend for treatment. The remaining 53 had a full course of treatment, and every one attended later for assessment of the results, so we have a 100% follow-up.

At the outset of this investigation the problem of a control series was discussed. It was considered that as so many variable factors were concerned, such as the age, weight, and general physical condition of the patients, and the type of arthritis, its severity, and the activity or quiescence of the disease, very large numbers of patients would be required to provide reliable comparisons. The treatment of bilateral affections where one side could be treated by the salicylate injection and the other by, for example, the oily base alone is possibly better scientifically, but was abandoned for practical considerations. It was therefore decided to use the patients themselves as their own controls. On the first examination, before treatment was begun, the assessor closely questioned the patients about the amount of pain and their various activities at the time and six months earlier. After treatment the same questions about pain and activity were asked again. Although this method results

in a comparison of subjective symptoms only, it gives a picture of the trend of symptoms without and with treatment in the same patients.

Treatment

All the patients were treated by intra-articular injections of benzyl salicylate in oil, given at weekly intervals for six weeks. Three knees received seven weekly injections, two knees eight injections, and five knees had two six-weeks courses. Eighteen knees received an intraosseous injection in addition to the six-weeks course, and one patient who had both knees treated had the course and two intraosseous injections. The indication for giving an injection into the bone was persistence of pain as the main symptom, after completion of the intra-articular course.

The solution used for the intra-articular injections was that used by Scott :

Benzyl salicylate	5%
Camphor	5%
Arachis oil	to 100%

It was used in doses of 0.1 to 0.3 ml., injected from a tuberculin syringe without an anaesthetic, or through an intradermal weal of procaine. If an effusion was present in the joint aspiration preceded the injection.

For the intraosseous injections the formula was :

Salicylic acid	0.2%
Sodium citrate	1%
Chlorbutol	0.5%
Phenol red	0.2%
Distilled water	to 100%

This solution was used in doses of 50 to 80 ml., the dose being divided between the femur and the tibia. In the femur the injection was given into the medial condyle below the adductor tubercle. In the tibia the site was the medial condyle two fingerbreadths below the joint line and just anterior to the tibial collateral ligament. The injection was given into the subcortical areas of the bones. Immediately before injection 150 turbidity-reducing units of hyalase were added to 100 ml. of the aqueous solution. A general anaesthetic is necessary, as this is a painful injection. If local tenderness was severe the periosteum in the tender area also was infiltrated with 1 to 5 ml. of the oily solution in divided doses.

Results

Of the 53 patients treated 12 were male and 41 female. Their ages ranged from 34 to 79, the average being 62. During treatment it was found that one patient was suffering from gout (blood uric acid 7.1 mg./100 ml.) and another from rheumatoid arthritis (E.S.R. 48 mm. in one hour, Westergren). Both these cases gave unsatisfactory results from the injections, but have been included in the survey and analysis as they were originally accepted, although they have weighted the results slightly on the unfavourable side.

While recognizing the difficulties of exact diagnosis, and the fact that some of the features of one type of arthritis may be present when the condition is, in the main, of another type, diagnoses were made as accurately as possible, and were as follows: primary generalized osteoarthritis (Kellgren), 27; osteoarthritis, 24; gout, 1; rheumatoid arthritis, 1. The number of knees treated was 88.

It was our intention to review the patients six months after completion of their treatment. However, some patients began their treatment later than was expected, and others had more prolonged treatment. In the whole series the average time between completion of treatment and re-examination was six months: for 42 knees it was less, and for 46 more than six months. A detailed clinical analysis (Table I) was made in each case before and after treatment, along the lines described by Shepherd (1954).

Five categories of *pain* were recognized: (1) none, (2) slight enough to ignore, (3) patient makes concessions to the pain, (4) pain causes disablement, (5) pain is absolutely crippling (see Table II).

To estimate *function* a series of questions on everyday activities were put to the patient. These elicited the distance a patient could walk, and the type of aid, if any, required in walking; the ability to use stairs, to kneel, to put on shoes, to take a bath; and the patient's usual work or activities in general. Inability to perform these actions in part or entirely was shown in the record by placing a black mark or marks against the action. The sum of these marks is a method of comparing function—the higher the number of marks the worse the function (see Table III).

Physical signs—heat, tenderness, effusion into the joint, and range of movement (Table IV)—were noted.

The *patient's own assessment* after treatment was classified as "enthusiastically pleased" in 35 cases, "pleased" in 29, "doubtful about the value" in 15, and "considered not worth while" in 9.

TABLE I.—*General Condition of 88 Affected Knees*

Alteration in 6 Months Prior to Treatment				After Treatment—Graded Results			
Better ..	4	Improved	6	Excellent	24	Improved	67
Slightly better	2			Good ..	27		
				Fair ..	16		
Same ..	35	Same or worse	82	Poor ..	21	Same or worse	21
Slightly worse	28						
Worse ..	19						

TABLE II.—*Pain*

Alteration in 6 Months Prior to Treatment				Alteration after Treatment			
Better ..	10	Improved	10	Very much better	15	Improved	68
				Much better	34		
				Better	19		
Same ..	45	Same or worse	78	Same ..	17	Same or worse	20
Worse ..	33			Worse	3		

Very much better = Two or more categories better. Much better = One category better. Better = Same category, but patient says better. Worse = Same category, but patient says worse.

TABLE III.—*Function by Performance*

Alteration in 6 Months Prior to Treatment				Alteration after Treatment			
Better ..	3	Improved	3	Very much better	7	Improved	55
				Much better	29		
				Better	19		
Same ..	48	Same or worse	85	Same ..	33	Same or worse	33
Worse ..	37			Worse	0		

Very much better = Seven or more black marks less. Much better = Three to six black marks less. Better = Two black marks less.

TABLE IV.—*Movement (After Treatment)*

Worse		Same (Within 10°)	Better	
Decreased by 10–19°	8	56	Increased by 10–19°	10
,, ,, 20–29°	1		,, ,, 20–29°	9
,, ,, 30–39°	1		,, ,, 30–39°	2
			,, ,, 40–49°	1
Total ..	10	56		22

The classification of results has been calculated according to a definite scheme, taking into account these four criteria —pain, function, physical signs, and the patient's own assessment. This scheme has been devised and strictly enforced to ensure that there is no tendency to overestimate in the tables the benefits of the treatment—rather the reverse. The overall grading of results (Tables V–VIII) may be broadly defined as follows: *excellent* (very marked improvement); *good* (marked improvement); *fair* (improved—in the assessor's opinion the treatment has been worth while); *poor* (minimal or no improvement—in the assessor's opinion the treatment has not been worth while).

TABLE V.—*Diagnoses and Grading*

Diagnosis	Grading After Treatment			
	Excellent	Good	Fair	Poor
Primary generalized osteoarthritis	17	17	4	10
Osteoarthritis	7	10	10	9
Rheumatoid arthritis			2	
Gout				2
Total	24	27	16	21

TABLE VI.—*Sex and Grading*

	Excellent	Good	Fair	Poor	Total
Male	3	5	4	5	17
Female ..	21	22	12	16	71

TABLE VII.—*Ages and Grading*

Ages	Excellent	Good	Fair	Poor	Total No. of Knees
Over 70 ..	13	7	2	10	32
60–69	5	6	10	8	29
50–59	4	11	3	3	21
40–49	2	3	—	—	5
30–39	—	—	1	—	1

TABLE VIII.—*Length of History and Grading*

Length of History	Grading				
	Excellent	Good	Fair	Poor	Total
Under 3 years..	13	11	13	9	46
Over 3 ,, ..	11	16	3	12	42

Comment

All the patients had, of course, come to hospital for treatment of their knee-joint disability. Very few therefore had improved during the six months before treatment. Allowance must be made for the fact that patients desiring treatment are not likely to minimize their complaints, while after any kind of treatment they are inclined to state that they have improved, even though this be really only evidence of wishful thinking.

The figures in the Tables do not represent scientifically accurate comparisons, but they suffice, we think, to indicate that there is value in the treatment.

The treatment itself is not pleasant, causing a temporary exacerbation of local symptoms and also considerable general malaise in many cases. If this is borne in mind, the patient's own assessment is of significance.

Function by performance was often more an index of general fitness than an indication of the function of the knee-joint. For example, a stout, almost blind, and very deaf old lady of 76 was wheeled up in her chair for both pre- and post-treatment examinations. She was very pleased with the results of the treatment. Pain, from having been of disabling severity in both knees, was reduced to none at all in one knee and to a negligible amount in the other. One knee had improved more than 20 degrees in its range of movement. Though this had made her much more comfortable, little change in function was possible owing to her other disabilities.

No significant difference was detected in the results between the group of cases who had completed treatment more than six months before the assessment and those treated less than six months before. No significant changes were found in pre- and post-treatment radiographs.

Eighteen knees received intraosseous injections after completing the standard course of intra-articular injections. The graded results in these were very similar to the graded results of the whole series shown in Table I.

All cases had clear radiological evidence of osteoarthritis, and the assessment of results has been based on strict criteria. In Table I a "fair" result indicates some improvement in the assessor's opinion, and on this basis 67 out of 88 knees were improved by treatment, yet only six had improved in the six months before treatment. Pain was definitely less in 68 of the knees treated, but in only 10 over the period of six months prior to treatment. If the two cases of gout and rheumatoid arthritis are excluded, as they should have been by more careful differential diagnosis before treatment, the results become even more impressive. The fact that every patient treated was prepared to attend again for reassessment several months later is significant: many had to travel considerable distances to do so.

Discussion

Is it possible to give some reasonable explanation of how this benefit has been produced? The improvement cannot be due to a simple local analgesic effect, as it did not occur until at least 24 hours after the intra-articular injection and was usually not noticed until after the third or fourth injection. Sometimes it was even postponed until after an intraosseous injection. When pain is relieved the patient is able to use the knee more. Function is in itself an aid to further recovery.

Scientific attention has recently been focused on the action of salicylates. Trethewie (1951, 1954) threw much light on the possible reasons for their effectiveness in rheumatic disorders. He proved that sodium salicylate and acetylsalicylic acid inhibit the release of histamine and similar substances. Apart from the importance of this work in relation to allergic phenomena it may well be that histamine or histamine-like substances resulting from tissue breakdown play a part in the production of symptoms in osteoarthritis. The ingestion of salicylates by mouth might well relieve symptoms in osteoarthritis by retarding the production of histamine-like substances, but a very large dosage would be required continuously to secure their inhibition. Local injection produces a high concentration of the salicylate at the point where its action is required. Scott (1938) showed that the use of oil as a solvent greatly slowed the absorption and excretion of salicylate.

The intraosseous injection probably acts both generally and locally. There is undoubtedly a rapid flooding of the blood stream with salicylate. Harrison and Gossman (1955) showed by experimental work that this happens in the cadaver. In living subjects the rate of entry into the larger veins must be even more rapid. An opaque injection was shown by the same authors to fill up a network of small veins surrounding the adjacent joints. From periarticular veins and venules the salicylate may exert a local effect. A similar local spread has been described by Heald (1951).

The clinical results in our series appear to justify further investigation of this method, which it is hoped this paper may stimulate.

Summary

A review is given of solutions which have been used in the injection treatment of osteoarthritis, and of the results obtained by their use.

Laughton Scott's methods of intra-articular and intraosseous injection are described.

The clinical results in 88 osteoarthritic knees in 53 patients treated by this method are analysed by an assessor not concerned in either the selection of the cases or their treatment.

The results obtained by this method appear to be encouraging.

The possible mode of action of the solutions used is discussed.

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THIOPENTONE SENSITIVITY AND DYSTROPHIA MYOTONICA

BY

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Since its introduction to clinical practice in 1934, thiopentone has come to be used universally on a very large scale for the induction of general anaesthesia and also as the sole anaesthetic agent for certain short operative procedures. After initial setbacks the common dangers attendant upon the use of the drug are now well appreciated. These dangers are many, and anaesthetists have written at length concerning the use and abuse of thiopentone. In addition to the common dangers there are a number of rare conditions which put the patient at risk when thiopentone is used. Amongst these may be mentioned porphyria, myasthenia gravis, Addison's disease, and dystrophia myotonica.

Dystrophia myotonica is a rare disease, but many practitioners must know of cases amongst their patients, and, in spite of its rarity, it is felt that the extraordinary sensitivity towards thiopentone shown by subjects with this disease should be brought again to the attention of all who are in the habit of using the drug.

The literature contains reference to only four instances of the use of thiopentone in dystrophia myotonica. A further case is recorded, and I have knowledge of two other persons who suffer from the disease.

Dystrophia Myotonica

Dystrophia myotonica is a hereditary familial disease affecting both males and females and usually appearing between the ages of 15 and 35 years. It does not of itself materially shorten life, but death usually occurs during the fifth decade from intercurrent infections. The features of the disease can be grouped under three heads.

1. *Myotonia.*—An involuntary persistence of muscular contraction following its voluntary initiation. It may be present in any group of muscles and is intensified by acetylcholine and by neostigmine and potassium.

2. *Muscular Atrophy.* — This quite characteristically involves the sternomastoids and facial muscles. Also involved may be the muscles of the shoulder-girdle, forearms, and hands, the quadriceps femoris, and the leg muscles below the knees. The atrophy is usually symmetrical on the two sides of the body; the affected muscles are weak but show no fibrillation. Tendon reflexes are diminished or absent. The rate of development is variable, usually proceeding over a period of some years, but it may be much more rapid. The wasting bears no constant relationship in either time or site to the myotonic symptoms.

3. *Others.*—Cataract appears in about 50% of cases, and may be seen in otherwise healthy siblings of those who show the muscular changes. It tends to appear at an earlier age in successive generations. Premature frontal baldness is a common feature, as also are ovarian and testicular atrophy. Less frequently seen are adenomata of the thyroid, diabetes mellitus, and abnormalities of the pituitary and adrenals. Mental changes are often present.

Histologically the disease has been shown to be confined entirely to the muscles; neither the central nor the peripheral nervous system shows any abnormality. There is no uniform atrophy of muscle fibres; healthy and degenerating fibres are seen side by side. Some fibres appear larger than normal, and in the early stages of degeneration show loss of transverse striation with proliferation of sarcolemmal nuclei; eventually the fibre is completely replaced by fat and connective tissue.

Diagnosis of the developed case is simple. When myotonia precedes muscle-wasting, the age of onset will distinguish it from Thomsen's disease (myotonia congenita). In the absence or late development of myotonia, the sternomastoid wasting is characteristic.

No treatment will arrest the progress of the disease. Quinine, 10–30 gr. (0.65–2 g.) daily is said to improve the myotonia, and the use of procaine amide has been reported (Geschwind and Simpson, 1955).

Case History

A woman aged 30, who had suffered from dystrophia myotonica for 14 years, had the classical features of myotonia and facial and sternomastoid wasting, and was of above average intelligence. She was to undergo an abdominal operation. Premedication, given one hour pre-operatively, with pethidine, 100 mg., and scopolamine, 1/150 gr. (0.43 mg.), did not appear to have unduly depressed her in any way. General anaesthesia was induced with 2.5% thiopentone, and a dose of 100 mg. was given. This dose produced loss of consciousness and apnoea, the latter lasting for 20 minutes, and thereafter respirations remained depressed for a further 20 minutes. The apnoea was accompanied by a state of complete muscular flaccidity comparable to complete curarization—direct laryngoscopy being easily possible. The quality and rate of the pulse remained unaltered during inflation with nitrous oxide and oxygen, and there was nothing to suggest wakening. Subsequently the response to D-tubocurarine was normal.

Discussion

This case, which was referred to by Langton Hewer (1957), corroborates the experiences of the three authors who have previously reported the idiosyncrasy. Dundee (1952) reports three cases, and Bourke and Zuck (1957) the fourth.

It has been found that in dystrophia myotonica normal doses of thiopentone cause profound depression of respiration amounting to apnoea. Doses of 500 mg. produced apnoea lasting 10 minutes in one of Dundee's cases, and lasting two hours in Bourke and Zuck's case; in both there followed a prolonged period of depressed respirations insufficient to maintain adequate oxygenation. These three authors were also able to show that so small a dose as 50 mg. of thiopentone produced a very marked depression of respiration almost amounting to apnoea, without producing loss of consciousness. The normal transient initial stimulation of respiration is not seen.

It is not intended to suggest that the use of thiopentone should be abandoned for this type of patient, though it is possible that some of the unexplained deaths occurring during thiopentone induction and anaesthesia could be attributed to this hypersensitivity. It is intended rather to point out the hazards, to emphasize certain basic principles, and to suggest that this rare disease may not in fact be exceedingly rare. To suspect every case of premature baldness or thyroid adenoma may be overcautious, but the

routine taking of family histories should not be omitted. Bourke and Zuck point out the significance of the high incidence of cataract in these patients and the modern trend towards general anaesthesia for ophthalmic surgery. Particular care should be taken, when thiopentone is used for dental extractions in the chair, to be on the look-out for respiratory depression after unusually small doses. A means of ventilating the patient should always be at hand. The possibility of meeting a case of dystrophia myotonica in these circumstances, among other reasons, should discourage any but the most experienced from administering thiopentone in the dental chair.

In the United States thiopentone is more widely used as a 2.5% solution than in this country. There is much to recommend this practice and little, if anything, to condemn it. In known or suspect cases of dystrophia myotonica a dilute solution, not stronger than 2.5%, should be used and a dose of 100 mg. has been recommended: respiratory depression seems to be inevitable, and with doses smaller than 100 mg. there is the chance that loss of consciousness may not result. Apparatus for the artificial inflation of the lungs must be at hand, and Dundee recommends inflation with nitrous oxide and oxygen rather than oxygen alone, because of the possibility of a return to consciousness whilst apnoea persists. If it is desired to intubate the trachea, this will usually be found possible without the use of a relaxant.

I am indebted to Dr. C. Langton Hewer for his advice, and to Mr. John Beattie under whose care the case described was treated.

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EFFECTS OF NYDRANE ON EPILEPSY IN MENTAL DEFECTIVES

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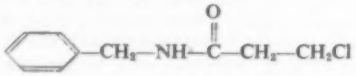
Notwithstanding the claims made concerning the efficiency of many of the recently introduced anticonvulsant drugs, epilepsy still remains a considerable medical and nursing problem. This is confirmed by Tredgold (1952), who states that fits occur in 11% of the feeble-minded, in 42% of imbeciles, and in 56% of idiots.

We decided to investigate the effects of a recently introduced anticonvulsant known as "nydrane." This drug is a benzylamide, N-benzyl-β-chloropropionamide, known in England as nydrane, in the U.S.A. as "hibicon," and on the Continent as "posedrine." It differs considerably from both the barbiturates and the hydantoins, having the structural formula:



It is a white crystalline solid with a molecular weight of 197.6 and a melting point of 94° C. The preparation is marketed in tablet form, the tablets being 0.5 g. in weight.

Previous clinical trials in Great Britain have been carried out by Hoenig *et al.* (1956) and by Robinson (1957), while Hawkes (1952) and Merlis and Martin (1956) have reported on its use in the U.S.A. There are also numerous references to its use in France and Italy.

Clinical Trial

We must emphasize that our primary aim was to discover whether this drug was objectively useful in the management of the chronic epileptic patient. We have divorced ourselves from the intricacies of the E.E.G. and concentrated on the reported day-to-day clinical state of the patient. We may stand condemned for issuing a report on an anticonvulsant without accompanying E.E.G. evidence. Surely the fact remains that with a chronic epileptic, especially in these days of staff shortages, what we wish to know is not his E.E.G. pattern but whether we have stopped or controlled his convulsions.

We may summarize our aims as follows: (1) to discover whether grand-mal epilepsy reacts favourably or otherwise with this drug; (2) to observe any change in behaviour and general conduct of the patient; and (3) to observe if any toxic effects are produced during the course of the trial.

Method and Material.—The clinical material used was 25 certified mentally defective patients of Botleys Park Hospital. They were all males aged from 17 to 50 years. Their I.Q.s ranged from 30 to 80. Eighteen of the cases were labelled as idiopathic epilepsy, six were of the traumatic type, and one of epiloia. All the cases demonstrated chronic grand-mal seizures and had previously been treated with barbiturates, phenytoin, and primidone, either singly or in combination. The method of control was similar to that carried out by one of us in a previous trial, using primidone (Sharpe, 1954)—namely, the patient acted as his own control in that an accurate assessment of his previous fit record and conduct was obtained from scrutiny of the patient's own epileptic record chart.

Dosage.—The scheme of dosage followed closely on that of other workers—namely, it is additive in the first instance, and finally any other anticonvulsants are replaced with nydrane. Irrespective of what previous drugs were being used, 0.5 g. of nydrane a day was added to the patient's treatment for the first seven days. Following this, the previous anticonvulsants were gradually withdrawn and substituted by 0.5 g. of nydrane weekly until the maximum dose was reached. In this series the maximum maintenance dose was found to vary from 3 to 4 g. a day, and usually this was divided into three equal parts. In practice we started withdrawing the hydantoins first and then gradually withdrew the barbiturates. We did attempt to control the epilepsy with nydrane alone. Unfortunately, this was found to be impossible, as in all except three cases a maintenance dose of barbiturates had to be given. The full course of treatment lasted for six months.

Toxic Effects

As nydrane is a relatively new and little-used drug in this country we decided to investigate thoroughly its possible toxic effects after prolonged usage, bearing in mind that we were subjecting our patients to large doses over many months. The scheme of investigation was as follows.

Pre-treatment.—Full blood count, Hb, R.B.C., W.B.C. and differential. Urine examination for albumin by the salicylsulphonic acid test, Benedict's qualitative test for reducing substances, and an examination of the centrifuged deposit.

During Treatment.—Weekly: routine examination of the urine as above. When reducing substances were found these were subjected to further examination to identify them. "Tes-tape" was used to detect glucose. The non-glucose reducing substances were subjected to paper chromatography and compared with known marker substances. Monthly: routine blood counts, Hb, W.B.C. and differential. After three and six months; serum proteins were estimated

by the biuret method and blood urea by the Nesslerization method; the formol-gel and Kunkel zinc sulphate flocculation tests were also done.

Results

Since we were looking for any possible toxic effects from the use of nydrane, results of the laboratory investigations are given separately as follows. *Haemopoietic system:* No evidence of disturbance was observed, there being no significant fall in the haemoglobin content or white-cell count. *Liver function:* This was apparently normal after three and six months of treatment. *Renal function:* At some time during the six months three cases showed a copper-reducing substance which was regarded as of no significance; six cases showed a trace of albumin, which in every case was only transient and cleared up even on continuation of treatment.

The blood urea of four cases showed a slight elevation above 40 mg. per 100 ml.—namely, 54.1, 42.8, 47.4, and 48.2 mg. per 100 ml.

Epilepsy and General Behaviour

In order to simplify the analysis of results of the treatment, with particular reference to grand-mal epilepsy, the following scheme was adopted. The basis of this is the percentage increase or decrease in the number of fits during six months under treatment with nydrane as compared with the previous number over a similar period before using the drug. Patients were recorded as being worse if they showed more than 25% increase in their fits during treatment. Where they showed a reduction of more than 25% they were regarded as improved, while those showing an increase or decrease of not more than 25% were regarded as showing no change.

Table I summarizes the results of the effect of nydrane on grand-mal epilepsy. Applying the χ^2 test of statistical

TABLE I

Grand-mal Attacks	No. of Cases	Percentage
Worse	3	12
No change	5	20
Improved	17	68
Total	25	100

analysis we have three alternative hypotheses. If we expect that 25 out of the 25 patients should be improved by nydrane medication, the χ^2 after applying Yates's correction is 2.25; postulating, however, that there would be no change in any of the 25 patients, the χ^2 after correction is 15.21; and postulating that all 25 patients will be made worse the χ^2 is 18.45. These figures would appear to indicate, therefore, that the first of the three hypotheses is more likely to be correct than either of the other two, and our results in obtaining 17 improved cases out of 25 on nydrane treatment are statistically significant.

The influence of the drug on the patients' general behaviour was recorded as 2 definitely worse (8%); 15 showed no appreciable change (60%); 5 showed a slight improvement in having a more co-operative attitude (20%); and 3 showed much improved conduct (12%).

When dealing with mentally retarded patients it is always valuable to correlate results with I.Q. range. This was carried out, and the results are shown in Table II.

Applying the χ^2 test to two I.Q. ranges of 30–49 and 50–70+, and omitting those with I.Q. below 30 because there were fewer than 10 of them, we have four possible hypotheses. In respect of those with I.Q. 30–49, and applying Yates's correction in all cases, postulating that nydrane will make all patients worse we get a χ^2 of 9.02; postulating that nydrane will effect no change we get 4.22; postulating that the drug will improve all cases, χ^2 becomes 1.22; and postulating that it will suppress all seizures we get 7.22. These figures clearly indicate that the assumption that nydrane will improve all patients is more correct than the other hypotheses.

TABLE II

Results	I.Q. Range		
	Below 30	30–49	50–70+
Worse	0	0	2
No change	0	3	2
Improved	4	6	4
No fits	0	1	3
Totals	4	10	11

Similarly, for the group with I.Q. 50−70+ we get figures for the χ^2 test corrected of 6.56, 6.56, 3.84 and 5.12. These indicate some preference for the hypothesis that patients on nydrane in this I.Q. range will be improved, but improvement is not so marked as in the lower I.Q. range above.

Discussion

It will be clearly evident from a perusal of the above results that nydrane exerts a marked anticonvulsant action in grand-mal epilepsy. The results which we have recorded compare favourably with those of Hawkes (1952), who found that 39 out of 59 patients had adequate control of convulsive seizures when given a clinical trial with hibicon. Similar, too, were the observations of Hoenig *et al.* (1956).

When comparing our results it must, however, be remembered that our clinical material, far from being of the neurological out-patient variety (as were the cases used by Hawkes), consisted of very chronic in-patients, several of whom were deteriorated and resistant to the usual therapeutic drugs—the worst possible cases.

We observed no attack of status epilepticus as mentioned by Hoenig *et al.*, but did notice an increase in excitability together with an increased incidence of convulsions during the transitional period. This was especially marked on withdrawal of the barbiturates, and, as has already been seen, in only three cases were we able to control the seizures without the use of barbiturates. It was found that the two drugs appear to be synergistic in their action, as our average daily dose of phenobarbitone was found to be reduced. We understand that nydrane combined with phenobarbitone is now available (nydrane co.).

In consideration of the results of the comprehensive investigations of toxicity carried out by one of us (G. D.) we make the following comment. It would appear from laboratory investigations that slight impairment of renal function was evident in some cases. This, however, was only transient and cleared up in spite of continuation of treatment. However, it must be borne in mind that in some cases we were using large dosages, up to 4.5 g. daily over a period of several months. It would therefore be wise to show caution in using large doses of nydrane over prolonged periods.

Turning to the clinical field, there was a notable freedom from signs and symptoms of toxicity apart from one patient who developed a temporary ptosis which we regard as being unconnected with the use of the drug.

Comment is worth while concerning the influence of the drug on the general behaviour of the patient. Chronic epileptics are well known to be a problem in this respect. We think it significant that 8 of our 25 patients did show some definite improvement in general behaviour. The relationship of the degree of control of fits to the mental state in general and to the emotional state in particular is difficult to reduce to figures. There was, however, a definite clinical impression that in some cases reduction of nydrane dosage during the course, with consequential slight increase in frequency of convulsions, resulted in improvement in general conduct and emotional stability. In a sense this probably implies previous overdosage and supports the view that, with nydrane as with certain other anticonvulsants, optimum dosage is not necessarily that which produces the greatest reduction in convulsions, but rather is the dosage which brings about the greatest improvement in the total clinical picture.

Our conclusions are that nydrane is of use in the control of chronic grand-mal epilepsy from the point of view both of reducing convulsion rate and of improving the patient's general behaviour.

Summary

A series of 25 cases were treated with nydrane over a period of six months.

In relation to grand-mal convulsions, 68% improved, 20% showed no change, and 12% were worse.

General improvement in behaviour of varying degrees was shown in 32%.

Transient renal disturbances were found in some cases.

We thank Dr. J. M. Crawford, physician-superintendent of Botleys Park Hospital, for permission to publish this paper. We are grateful to Dr. S. Phillips, of Rona Laboratories Ltd., for the supply of the drug used in this trial.

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Medical Memoranda

Ear Presentation : A Case of Transverse Arrest at the Outlet

With improved antenatal care malpresentations and abnormal labours are becoming more rare, and a description of a case of ear presentation is of interest, if only on account of its extreme rarity. I have found only one similar instance in the literature (Walker, 1928).

CASE HISTORY

A primigravida aged 25 attended the antenatal clinic from December 12, 1956, until her confinement, her estimated date of delivery being April 26, 1957.

At the thirty-fourth week she developed signs of toxaemia and was admitted to hospital for rest and observation. Her condition remained *in statu quo* until the thirty-seventh week, when an increase in the blood pressure and the appearance of albumin in her urine suggested a deterioration. Therefore on April 9 labour was induced by low artificial rupture of the membranes. The cervical os was tight, and at this time the cervix was hardly taken up. Presentation was confirmed as right occipito-anterior. Although she experienced fairly strong pains soon after this procedure, labour in the first stage was rather intermittent,

FIG. 1.—Showing relationship between foetal skull and maternal bony pelvis.

seven days elapsing before full dilatation was complete. The presentation during this time varied between right occipito-anterior and right occipito-lateral.

At 8.30 p.m. on April 17 dilatation of the cervix was complete, and the second stage began with a midwife in attendance. By 9.30 p.m. little advance had been made in the presence of strong and regular contractions, the head being fixed low in the cavity. Vaginal examination revealed an ear presentation, and this could be confirmed visually by separation of the labia and slight retraction at the introitus (see Fig. 1).

Procedure.—With the patient under general anaesthesia and in the lithotomy position the following situation was found. The left ear was presenting, the occiput on the right, the anterior fontanelle lying postero-laterally to the left. The head was firmly wedged into the lateral walls of the pelvis. Posteriorly there was plenty of room between the bregma and the sacral curve, and the posterior (right) shoulder was impacted in the midline under the promontory, closely in apposition to the right ear. The head could not be pushed up. With the right hand in the sacral curve the posterior shoulder was disengaged from the promontory and passed to the right, thus bringing the back of the foetus round more anteriorly. The head was then pushed up, the occiput disengaged from the symphysis and swept downwards and forwards, flexing the head and rotating it into the right occipito-anterior position. Delivery was achieved by forceps extraction; the placenta, separating after the manner described by Matthews Duncan, was delivered by Credé's manœuvre.

The mother had a normal puerperium, although she had a slight thrombosis in the left leg a week after delivery.

The Mother.—Height 5 ft. 8 in. (173 cm.). Weight 12 st. 6 lb. (79 kg.). Pelvimetry: Angle of inclination of the brim 40 degrees. Measurements:—At the brim: true conjugate, 5.6 in. (14.2 cm.); transverse diameter, 5.2 in. (13.2 cm.); both oblique diameters, 4.85 in. (12.3 cm.). At mid-cavity: antero-posterior diameter, 6.4 in. (16.2 cm.); transverse diameter, 4.5 in. (11.4 cm.). At outlet: Antero-posterior diameter, 5.3 in. (13.5 cm.), transverse diameter, 5.0 in. (12.7 cm.). The radiologist's report: "This is a large symmetrical pelvis with much available space in the mid-cavity in the antero-posterior diameter. A fairly small angle of inclination of the brim and no obvious promontory are noted."

The Baby.—Born alive. Weighed 5 lb. 1 oz. (23 kg.) at birth. Moulding was minimal. There was no caput succedaneum, or any deformities. The infant's general condition at birth was excellent. Cephalometry:—Diameters: occipito-frontal, 4¼ in. (10.8 cm.); suboccipito-bregmatic, 3½ in. (8.9 cm.); biparietal, 3⅝ in. (9.2 cm.). Circumference: occipito-frontal, 13½ in. (34.3 cm.).

Postulated Mechanism.—(1) At the beginning of the descent the foetus was in a completely right occipito-lateral

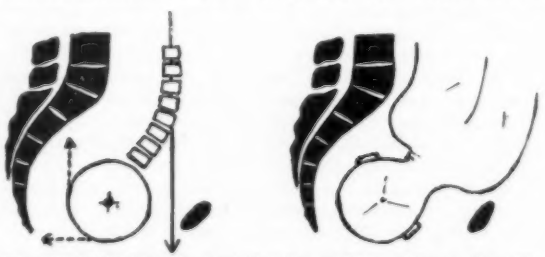

FIG. 2.—Right lateral aspect showing position of foetus immediately before correction of malpresentation. Diagram on left illustrates mechanism; expulsive forces represented by continuous line, resultant acting where foetal skull is in contact with side walls of pelvis/pelvic floor by dotted line.

position with the head deflexed. (2) As the head came down into the flat pelvis, anterior asynclitism developed, the head remaining deflexed. (3) Absence of "bite" between the head and the pelvic walls due to the relatively small size of the head resulted in failure of internal rotation and flexion. (4) The shallowness of the brim and absence of an

obvious promontory permitted the axis of the expulsive forces to lie nearly vertical, thus resulting in increase in the lateral flexion of the head (see Fig. 2). (5) The antero-posterior depth of the cavity was such that the deflection of the head by the sacral curve and consequent correction of asynclitism could not take place until the posterior shoulder was impacted against the sacrum. By this time the head was so wedged against the lateral pelvic walls that spontaneous correction and delivery had become impossible.

COMMENT

That the malpresentation described above is extremely rare seems to be due to the factors involved in its production. These are: (1) the relatively small baby; (2) a relatively roomy pelvis, particularly in the antero-posterior diameter; and (3) a low angle of inclination of the pelvic brim.

No opinion can be formed concerning the part played by the musculature of the pelvic floor in the mechanism of this presentation, since in the case described by Walker (1928) the mother was a 2-para. It is not certain that there is any significance in the lateral siting of the placenta.

The manipulation described, carried out under general anaesthesia, resulted in the effortless forceps delivery of a live infant.

I am indebted to Mr. D. J. P. O'Meara for permission to publish this case, and to Dr. S. Mitra, consultant radiologist, for his help with the pelvimetry.

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Acquired Mucocele of the Gall-bladder in Childhood

Acute disease of the gall-bladder is uncommon in childhood. The following two cases occurred in children under the age of 4 years admitted to Cardiff Royal Infirmary. One case has already been described by Narat (1940).

CASE 1

A boy aged 24 months was admitted as an emergency. He had been quite well until four days before this, when he started to vomit. Next day he appeared to have attacks of colic, which caused him to pull up his knees when lying down; these attacks of pain persisted until he came to hospital. During this period three or four bowel evacuations occurred daily, the stools being loose and yellow.

On examination his temperature was 97.6° F. (36.4° C.), pulse 74, and respirations 24. The child was pale and lay quietly in his cot, sleeping fitfully; his tongue was furred. Abdominal examination was not resented except for palpation in the right hypochondrium; here there was marked guarding, and when this was relaxed during the brief intervals of sleep a mass could be felt extending for 1 in. (2.5 cm.) below the inferior margin of the right lobe of the liver, but not extending to the midline. Rectal examination was negative. Barium enema showed a filling defect in the transverse colon near the hepatic flexure.

It was decided to explore the abdomen on account of the presence of the tender mass. At laparotomy by right paramedian para-umbilical approach the gall-bladder was found to be tensely distended and injected. It could not be emptied by compression, and when aspirated to facilitate exposure of the cystic duct 45 ml. of faintly bile-stained mucus was withdrawn. Dissection in the free border of the lesser omentum revealed a fine pale atretic cystic duct. The hepatic and common bile ducts were pale and narrow; and adjacent to the common bile duct above the duodenum was an enlarged lymph node. Cholecystectomy was performed. Post-operative progress was uneventful and the child was discharged on the ninth day.

Histologically the gall-bladder showed acute inflammatory changes. The small fragile cystic duct was too traumatized by the crushing clamps to yield useful material for section.

Conclusion.—The fundamental lesion here appeared to be a congenital atresia of the cystic duct associated with a lesser degree of atresia of all the extrahepatic duct system. Patency of the cystic duct was suggested by the faint bile-staining of the gall-bladder contents; otherwise it must have been due to a small accessory hepatic duct draining direct into the gall-bladder. The hepatic and common bile ducts were hypoplastic, and sufficient lumen must have been present, as the child was not jaundiced.

CASE 2

A boy aged 41 months; emergency admission. Three days before admission the child developed attacks of colicky abdominal pain, each of some five minutes' duration with remissions of about 15 minutes. On the following day he vomited several times. There was no change of bowel habit. Two years previously, at the age of 17 months, the child had been admitted to another hospital for investigation because he was failing to progress. At this time the duodenal juices showed absent tryptic activity. Fibrocystic disease of the pancreas was diagnosed and the patient treated with pancreatic extract.

On examination his temperature was 98° F. (36.7° C.), pulse 100, and respirations 26. The child was small for his age, and did not appear unduly ill. Abdominal examination revealed marked tenderness in the right hypochondrium, but no mass could be felt distinct from the liver, which was slightly enlarged. Rectal examination was inconclusive. A barium enema was performed, and, while no gross abnormality was found on screening, on one of the films taken the shadow of the transverse colon appeared to be indented near the hepatic flexure.

It was decided to explore the abdomen because of the history of pain and the presence of tenderness. At laparotomy, carried out by a right paramedian para-umbilical incision, the gall-bladder was found to be tensely distended, injected, and in some areas infarcted. It could not be emptied by compression, and, to facilitate manipulation, aspiration was performed, 45 ml. of viscid colourless mucus being withdrawn. The distension of the gall-bladder stopped short at the cystic duct, which, together with the other extrahepatic biliary ducts exposed by dissection in the free border of the lesser omentum, appeared entirely normal. Cholecystectomy was performed. Post-operative progress, apart from mild bronchitis, was uneventful.

On section the gall-bladder walls were found to be congested and oedematous, with several areas of infarction, but no cause of cystic duct obstruction could be found. Microscopically there were inflammatory changes consisting of eosinophil leucocyte infiltration and areas of fibrinoid necrosis, in some places involving the walls of the blood vessels.

Post-operative Investigations.—Blood: red cells, 4,960,000; haemoglobin, 63%; colour index, 0.6; white cells, 15,700 (polymorphs 79%, lymphocytes 11%, monocytes 10%). Urine: reaction, acid; albumin, nil; deposit, a very occasional leucocyte only. Fluid from the gall-bladder: a few pus cells and some debris; no organisms seen. Serum agglutinin titre: nil for typhoid O and H, paratyphoid BO and BH, and non-specific Salmonella H. Rectal swab: coliform colonies, rough and untypable. Stool culture: No pathogens isolated. Faecal tryptic activity: detected at dilution of 1:2,560. Duodenal juices: specimens 1 and 2, no tryptic activity detected; specimens 3 and 4, slight tryptic activity at dilution 1:1; all four specimens alkaline.

The fundamental lesion in this case was considered to be mucosis associated with mucus-plug obstruction of the cystic duct and fibrocystic disease of the pancreas.

I am most grateful to Mr. D. Ioan Jones and Professor A. G. Watkins for their advice and their permission to publish these cases.

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Reviews

RHEUMATOID ARTHRITIS

Rheumatoid Arthritis: A Definition of the Disease and a Clinical Description Based on a Numerical Study of 293 Patients and Controls. By Charles L. Short, M.D., Walter Bauer, M.D., and William E. Reynolds, M.D. (Pp. 480+x. 55s.) Cambridge, Mass: Harvard University Press. London: Oxford University Press. 1957.

This is a very remarkable book which should be widely noticed. It constitutes a scrupulous clinical study of the natural history of a common crippling disease from every aspect fortified by all the rites of modern science. It is written by three American physicians of great distinction, and is excellently produced by the Harvard University Press. It records in great detail an analysis of the clinical, pathological, and epidemiological observations on 300 patients with rheumatoid arthritis who were first studied in the wards of the Massachusetts General Hospital in 1929 and who have been regularly followed up subsequently. In view of the authors' belief that rheumatoid arthritis is perhaps the most important of diseases from the economic and social aspects, this interesting series is to remain under observation and further reports are promised for the future. These will be eagerly awaited.

The authors regard rheumatoid arthritis as an independent chronic inflammatory systemic disease of single, although so far unknown, origin. The manner in which joint involvement occurs is, in their opinion, highly significant, and is the object of close analysis. They make an elaborate study of the signs and symptoms encountered in this disease with a view to compiling a corpus of diagnostic criteria. For this purpose they use a numerically equal control group of non-arthritic patients, with the help of which they have evaluated certain aspects of the disease of which the significance has hitherto been in doubt. They also discuss in great detail and in searching fashion those forms of joint disease which should be considered as clinical variants of rheumatoid arthritis and those which should be deemed separate conditions. It is probable that a chronic disease of unknown aetiology has never hitherto been subjected to such scrupulous examination in its every aspect by such scientifically well equipped observers over such a long period. As a result, although the authors raise as many questions as they answer, the subject is much clarified. They succeed in classifying many specific elements of this disease, and of clarifying its relationship with other connective-tissue disorders with greater precision than hitherto was the case. Their study of the prodromal symptoms and signs and of the natural variations of the disease will be found particularly valuable to all rheumatologists and general physicians who are interested in this field of medicine. The only criticism one might make is that the authors tend to confuse several minor issues by regarding ankylosing spondylitis as a variant of rheumatoid arthritis, as is not uncommon in America.

This is not an easy book to read; the information contained is too concentrated. It is, however, summarized succinctly at the end in twelve pages and two appendices. There are also numerous tables and an extensive bibliography and index. It is the most important contribution to the study of rheumatoid arthritis which has appeared.

W. S. C. COPEMAN.

X-RAY DIAGNOSIS OF ABDOMINAL TUMOURS IN CHILDHOOD

Roentgen Diagnosis of Abdominal Tumors in Childhood. By Charles M. Nice, Jr., M.D., Ph.D., Alexander R. Margulis, M.D., and Leo G. Rigler, M.D. (Pp. 75+viii; illustrated. 30s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1957.

This book has a small range, but that does not prevent its being a most useful and much-needed one. It is particularly useful because, as the authors say, their work is "based on conventional, rather simple routine roentgen examinations available to everyone. . . . It is true that in certain instances special studies such as planigraphy, presacral CO_2 insufflation, aortography, spleno-portography, etc., are of value, but in the majority of cases they are not essential." On the frequent occasions when a small child arrives for a consultation suffering from a fairly obvious condition, and accompanied by a wad of *x*-ray films half an inch thick, the surgeon as he leafs through them may wish that this approach was more widely used.

In pursuing this line of diagnosis the authors make use of what philosophers might call the method of logical analysis. (In parenthesis it may be observed that in some of the older courses of medical education the study of logic was included: I do not know if this still survives somewhere, but, judging by medical meetings and publications, logic has been entirely superseded by experiment and tabulation.) They show that, by applying a knowledge of anatomy, embryology, and the various types of tumour which can occur to the analysis of the information given by straight radiographs and opaque fillings of the digestive and urinary tracts, useful and accurate information can be gained about the nature of the underlying condition—information that may make all the difference to the ease and success of surgery. The immense variety of cases discussed, and the extreme rarity of many of them, show that the book is the product of a very large experience of its subject. In fact it is rather tantalizing to a surgeon interested in the same line of work not to know what was done about many of them and what results were obtained.

It is hardly necessary to state, in reviewing a modern textbook from the U.S.A., that the paper, printing, and *x*-ray reproductions are excellent. What is, however, worthy of remark in a work from this source is that the writing is simple and easy to understand, with a welcome absence of the inflated and polysyllabic jargon of so much transatlantic medical writing.

DENIS BROWNE.

THE ORIGIN OF LIFE

The Origin of Life on the Earth. By A. I. Oparin. Third revised and enlarged edition. Translated from the Russian by Ann Synge. (Pp. 495+xviii; illustrated. 35s.) Edinburgh and London: Oliver and Boyd. 1957.

Medical men, dimly recollecting their premedical biology courses, may well be pardoned for doubting whether anything sensible and convincing could be written about an event so remote as the origin of life. It is not a hundred years since Louis Pasteur won a prize from the French Academy of Sciences for experiments which finally consigned the idea of spontaneous generation of living matter to the lumber room of scientific history; and that appeared to be the last word which bona-fide scientists would have to say on the origin of life. But recent advances in biological chemistry have reopened the question at a much higher level. The origin of life is a continuous process, going on in every organism which grows, absorbs non-living matter, and converts it into protoplasm. By modern methods it is possible to study the synthesis of proteins and other substances which comprise protoplasm; indeed, some stages in the synthesis can now be reproduced in the laboratory. Also by modern methods one can discover the sources of energy for the process of building up molecules of living matter. In the light of these recent researches the origin of life is no longer a matter for vague speculation, but has become a highly technical problem in biochemistry. What are the simplest organic materials capable of absorbing and utilizing solar energy? How could these materials have been synthesized in a world devoid of life? What is the biochemistry of evolution: that is to say, how did the physiology of the most primitive organic energy-fixers evolve into the physiology of modern organisms? These are the questions which Academician Oparin discusses in this greatly enlarged edition of his well-known work. The days are over when we complacently assumed that there was probably something "phony" about scientific books from

the Soviet Union. There is nothing "phony" about this book. It is a first-class biochemical detective story, well documented, and for the most part within the compass of a reader who has survived the biochemistry course in a medical school.

ERIC ASHBY.

AMERICAN TEXTBOOK OF SURGERY

Surgery: Principles and Practice. By J. Garrott Allen, M.D., Henry N. Harkins, M.D., Ph.D., Carl A. Moyer, M.D., and Jonathan E. Rhoads, M.D., D.Sc.(Med.). (Pp. 1,495+xxii; illustrated. £5 10s.) London: Pitman Medical Publishing Co., Ltd. 1957.

This encyclopaedic new work is a highly successful attempt to produce a national American textbook of surgery of the highest class. The 30 authors are representative of all that is best in modern American surgery. It is clear that they have been selected no less for their professional standing than for the clarity of their thinking and of their prose, and for their willingness to pull together in a team. All surgical specialties are included—and with them gynaecology—except for ophthalmology and oto-rhino-laryngology. The book is aimed primarily at the undergraduate medical student, and principle has always been in the forefront of the authors' mind rather than those surgical details which are learnt in a specialist postgraduate surgical programme. The clinical metabolic management of the patient, in which American surgery so excels, is treated in a masterly way by Francis D. Moore, and non-operative surgical care equally ably by Carl Moyer. Jonathan Rhoads is at his best in a consideration of fluid and electrolyte balance. Henry Harkins recapitulates those problems of shock for which he is so particularly notable, and Garrott Allen has covered a great part of the surgery of the abdomen. Even to mention these names is invidious, for, as not in all textbooks of multiple authorship, it can be quite clearly stated that the chapters are of equal excellence. The format of the book is most attractive and the publisher is to be congratulated on paper, binding, and print. The illustrations, not too numerous for a book of this size, are well chosen and clear. References are sufficient in number for an undergraduate student and are very representative, though predominantly American. It is clear that this volume will be a standard work for undergraduates, and any undergraduate would benefit from having it available.

IAN AIRD.

INFORMATION ON CANCER

The Truth about Cancer. By Charles S. Cameron, M.D. (Pp. 256; illustrated. 30s.) London: Hutchinson Medical Publications. 1957.

Any reader who anticipates that *The Truth about Cancer* will reveal some hitherto undiscovered fact or theory about cancer is in for a disappointment, for Dr. Cameron's message is that diagnosis at an earlier stage would double the proportion of lives of cancer patients which are at present saved by surgery and radiotherapy. Cameron strenuously advocates early diagnosis and treatment. No one can disagree with such advice, but when he urges the layman to undertake routine periodical self-examination, many readers would object that the effect would be more likely to produce cancer-phobia than the discovery of early cancer.

For the newcomer to the subject the book contains a good deal of information on the well-worn themes, all administered in a bland, bright style. The presentation hovers between the ghoulish and the grandmotherly. The colour photographs of cancers will horrify, or perhaps fascinate, a good many non-medical readers: the sedative generalizations will irritate those who have come to some definite conclusions on the disease. After piling up pages of evidence that cigarette-smoking is the main factor in the lung-cancer epidemic, Cameron soothingly concludes that:

"These questions and a lot of others still need to be answered before proof of the guilt of tobacco as a cause of lung cancer can be established beyond argument. Much research activity is now directed at getting at these answers. The question uppermost in the minds of scientists at the moment is whether the well-established and generally accepted statistical association between cigarette-smoking and cancer of the lung is one of cause and effect or whether it is incidental. It is possible that the tendency to smoke heavily and the tendency to get lung cancer are both the result of a common and as yet unidentified factor or cause. One such influence might be a distinctive type of hormone balance. It is known that hormones seem to be involved in the development of certain kinds of cancer, and it is conceivable, though far from proved, that hormone stimulation may be responsible for a high pace of living, carrying with it an intense desire to smoke. Explanations like this are pure speculation, but ways are being sought to put them to the scientific test. The final answer will probably be years in coming."

I. HIEGER.

B.C.G.

Advances in Tuberculosis Research. Edited by Hans Birkhauser and Hubert Bloch. Volume VIII. *BCG: A Discussion of its Use and Application.* (Pp. 316. 60s.) Oxford: Blackwell Scientific Publications. 1957.

This book constitutes a kind of international symposium on B.C.G. The authors of the various articles come from seven countries—Brazil, Denmark, Great Britain, France, Norway, Sweden, and the United States. For the most part the articles give a useful account of current knowledge, current practice, and current opinions. The contributions from this country consist of an assessment by P. D'Arcy Hart, T. M. Pollock, and I. Sutherland of the first results of the Medical Research Council trial of tuberculosis vaccines in adolescents, a summary by A. Q. Wells of the history and present position of the vole bacillus vaccine, and an account by D. A. Mitchison of the theoretical considerations in relation to the problem of prophylactic chemotherapy. The general balance of the book is good; unlike many publications on the subject, it does not present the views of enthusiastic advocates only. There is an account of untoward reactions, including a summary of the nine published cases of generalized tuberculosis resulting from B.C.G., and J. A. Myers has been given an opportunity of presenting a summary of his well-known views opposing B.C.G. The book can be recommended as a fair statement of the present position of B.C.G., with special reference to the many theoretical problems and practical controversies which remain to be resolved.

J. G. SCADDING.

An international conference on student mental health was held in Princeton, N.J., in 1956, and a bibliography—*Student Mental Health: An Annotated Bibliography 1936–1955*—was prepared for the members by D. H. Funkenstein and G. H. Wilkie, with the aid of the Grant Foundation and the Field Foundation. This was an attempt to evaluate the work in this branch of mental health in colleges and universities, and to consolidate present knowledge in order to assist in future planning. The bibliography (published for the World Federation for Mental Health by H. K. Lewis, Ltd., 136, Gower Street, London, W.C.1; 20s.) covers both books and articles, many of which have been abstracted. It does not include work on veteran or adult students, nor on students in specific faculties, but some articles on preventive mental health and delayed adolescence have been included where they are relevant to the student problem. There are over 1,800 entries, arranged alphabetically under authors, with a rather unnecessary author index. This should be a most useful reference work for those interested in student mental health.

Spastics in Cheyne Walk, by Joan Saunders and Marjorie Napier (Pitman Medical Publishing Co., Ltd., London, 1957; 20s.), is an account of the origin, layout, and work of the Centre for Spastic Children, Cheyne Walk, Chelsea. The centre was established in April, 1955, in the building formerly occupied by the Cheyne Hospital for Sick and Incurable Children.

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EXPERIMENTAL LINKS BETWEEN TOBACCO AND LUNG CANCER

The evidence for a causal relationship between smoking and carcinoma of the lung has been strengthened over the last eight years by refinement in survey of social habits and an analysis of clinical material,[1] so that the Medical Research Council[2] has felt justified in advising the Government that "a major part of the increase" in lung cancer is "associated with tobacco smoking, particularly in the form of cigarettes." The fact that experimental work has not provided complete and irrefutable proof of this conclusion has tended to hinder its whole-hearted acceptance; but the supporting evidence is growing, though in some respects the results are conflicting and not yet reconcilable with the whole clinical pattern of lung cancer in man.

Research has taken several forms, perhaps the most obvious being the exposure of laboratory animals to cigarette smoke; but here the results have been conflicting. Using mice, J. A. Campbell[3] found over 20 years ago that lung tumours were rather more frequent in the exposed than in the control groups. The numbers were small and the strains not so highly inbred as those now used, so that even his control groups showed considerable variation in incidence of tumours. R. Passey[4] found no such increased incidence in mice exposed for 16 months to tobacco smoke, nor did E. Lorenz and colleagues,[5] using pipe smoke and a strain of mice with a high spontaneous incidence of adenomas. With this same strain J. M. Essenberg,[6] using cigarette smoke, has shown a higher frequency of adenomas and adenocarcinomas. Recently J. W. S. Blacklock[7] injected into the hilum of the lung condensates of smoke obtained from a proprietary cigarette filter, passing the needle through the lung itself to avoid spilling and to increase retention of the condensate. He may have detracted somewhat from the relevance of this experiment by adding a small number of killed tubercle bacilli, though these are unlikely to be responsible for the tumours produced in two out of eight animals, in one a sarcoma, in the other a carcinoma.

Another method of examination, painting the skin of animals with the constituents of tobacco smoke and its residues, has shown their carcinogenic activity. For instance, A. H. Roffo[8] produced a carcinoma in the ear of a rabbit with a condensate of smoke from tobacco burned in a pipe, and also a skin tumour with tars obtained from heating tobacco. C. M. Flory,[9] in 1941, working with smoke condensates from tobacco burned in pipes without puffing, produced papillomas in rabbits but not in mice, a similar result to that obtained from cigar smoke by O. Schürch and A. Winterstein.[10] It remained for E. L. Wynder, E. A. Graham, and A. B. Croninger[11] to produce both papillomas and carcinomas of mouse skin using condensates of smoke from automatically puffed cigarettes (Roffo had not used so refined a technique). Papillomas developed in 59%, and carcinomas in 44%, of 81 mice. Though Wynder and his colleagues have detected varying susceptibility to carcinogens in different strains, they have produced some tumours in all three strains they have tested.[12] The specific substance or substances responsible for this effect have not been identified, though the active ingredients can be concentrated to 1.5% of the original amount of tar used. The skin-painting experiments of Passey,[13] R. H. Gwynn and M. H. Salaman,[14] and D. Hamer and D. L. Woodhouse[15] yielded negative results, but as they did not use the same methods of preparation and application their results are not comparable with those obtained by Wynder and his colleagues.[12] K. Sugiura,[16] on the other hand, following the same plan as Wynder, also succeeded in producing tumours. The discrepancy between the American and the British results is being further investigated.[15] A third means of investigation, chemical analysis of cigarette smoke, has shown that known carcinogens are present in it.

[1] Doll, R., and Hill, A. B., *Brit. med. J.*, 1956, **2**, 1071.
[2] Ibid., 1957, **1**, 1523.
[3] Campbell, J. A., *Brit. J. exp. Path.*, 1936, **17**, 146.
[4] Passey, R., *Extract from Reports and Accounts Yorkshire Council of the British Empire Cancer Campaign*, 1927.
[5] Lorenz, E., Stewart, H. L., Daniel, J. H., and Nelson, C. V., *Cancer Res.*, 1943, **3**, 123.
[6] Essenberg, J. M., *Science*, 1952, **116**, 561.
[7] Blacklock, J. W. S., *Brit. J. Cancer*, 1957, **11**, 181.
[8] Roffo, A. H., *Bol. Inst. Med. exp. Cancer (B. Aires)*, 1939, **16**, 255.
[9] Flory, C. M., *Cancer Res.*, 1941, **1**, 262.
[10] Schürch, O., and Winterstein, A., *Z. Krebsforsch.*, 1937, **46**, 414.
[11] Wynder, E. L., Graham, E. A., and Croninger, A. B., *Cancer Res.*, 1953, **13**, 855.
[12] —— Lupberger, A., and Grener, C., *Brit. J. Cancer*, 1956, **10**, 507.
[13] Passey, R., *et al.*, *Annual Report of the British Empire Cancer Campaign*, 1954, **32**, 60.
[14] Gwynn, R. H., and Salaman, M. H., quoted in *Annual Report of the British Empire Cancer Campaign*, 1954, **32**, 172.
[15] Hamer, D., and Woodhouse, D. L., *Brit. J. Cancer*, 1956, **10**, 49.
[16] Sugiura, K., *Gann*, 1956, **47**, 243.
[17] Cooper, R. L., Lindsey, A. J., and Waller, R. E., *Chem. and Ind.*, 1954, p. 1418.
[18] —— —— ibid., 1956, p. 1260.
[19] Kosak, A. I., *Experientia (Basel)*, 1954, **10**, 69.
[20] Satterlee, H. S., *New Engl. J. Med.*, 1956, **254**, 1149.
[21] Gilbert, J. A. S., and Lindsey, A. J., *Brit. J. Cancer*, 1956, **10**, 642.
[22] Cooper, E. A., Lamb, F. W. M., Sanders, E., and Hirst, E. L., *J. Hyg. (Lond.)*, 1932, **32**, 293.
[23] Wynder, E. L., and Wright, G., *Cancer (Philad.)*, 1957, **10**, 255.
[24] Andervont, H. B., *Publ. Hlth Rep. (Wash.)*, 1939, **54**, 1519.
[25] De Beer, G. R., *Proc. roy. Soc. B.*, 1947, **134**, 377.

For example, 3:4 benzpyrene has been detected in the smoke both from cigarette tobacco and from cigarette paper.[17 18] Arsenic, another known carcinogen, is also included[19 20] in the growing list of substances which have been identified.[21]

These experiments point to carcinogenic activity in the smoke produced during cigarette smoking. They also point to the preliminary necessity for establishing similar conditions in the experimental production of smoke as actually obtain during smoking. E. A. Cooper and his colleagues[22] have shown that the temperature can range from 370 to 700° C., and emphasized the importance of the higher temperature for producing carcinogenesis. Wynder and his colleagues[11] reported an average temperature of 682° C., with a maximum several hundred degrees higher, in the combustion of cigarettes from which they obtained smoke. Although skin tumours have been produced with increasing frequency, the production of tumours in the lung has been less successful. The results of the inhalation method, however, may be vitiated by the fact that inhalation of a substance into the lungs does not necessarily imply its retention, and retention, if it does occur, may vary in its site from species to species. Size of particle of the inhaled substance and flow of mucus are two other variable factors which may influence the retention of material in the lung and the production of tumours. Although known active carcinogens have been identified in tobacco smoke these are all in such small amount that Wynder and G. Wright[23] do not consider that those already recognized can account for the results of skin painting, and they believe that the effective substance has still to be isolated. In view of the amount of coal tar which was extracted to give suitable amounts of its active contents for study, the number of cigarettes which may be sacrificed by fire to this purpose will probably be fabulous.

When tumours have been produced in the lung they are usually sarcomas, adenomas, or less frequently adenocarcinomas, and not the squamous-cell type seen most commonly in man. Even the injection into the lung of benzpyrene and dibenzanthracene, known carcinogens of great potency, usually produces sarcomas. H. B. Andervont[24] produced a squamous carcinoma by a modification of the method of administration in which a thread coated with dibenzanthracene was threaded through the chest wall, probably thereby increasing retention of the carcinogen against the bronchial epithelium. The malignant nature and cell type was also established by transplanting. Malignant nature, proved either by metastasis or by transplant, may be more significant than cell type, since the nature of the tumour is probably related at least in part to the site of action of the carcinogen. Too much emphasis on cell type may occur if the pathologist attributes too great an exclusiveness to the germ layers.[25]

The evidence produced by the inhalation of tobacco smoke[6] and by painting condensates of smoke on skin,[11] or injecting them into lung,[7] in addition to the identification in this smoke of known carcinogens,[17] all points to the carcinogenic properties of tobacco smoke. And yet, even if all these experiments were uniform in their results, their findings could not be applied uncritically to the human story. Many details of the clinical picture will need to be reconciled before there is a comfortable fit between the epidemiological and laboratory findings. For instance, pipe smoking is not associated with as high an incidence of lung cancer as cigarette smoking, and yet the tar from pipe smoke has a higher concentration of carcinogens than that from cigarette smoke. Furthermore, in seeking for evidence of damage to the lung by tobacco smoke, it may be that the sign to seek is not the production of tumours. Smoking may make its major contribution in man by action which is more truly co-carcinogenic—for example, by allowing the entrance into and retention in the bronchial mucosa of more active carcinogens.

The findings of epidemiological survey stand separate and intact. In so far as they indicate a causal relationship between smoking and lung cancer they will not be invalidated by negative experimental results, but will be strengthened by corroborative support from work done in the laboratory, and it is from here that the major contribution will be made towards elucidating the nature of the relationship. Despite certain discrepancies such as result from differences between species and different methods of administration—features inherent in animal experiment—laboratory investigation still lends positive support to the epidemiological evidence while offering further stimulus to continued inquiry into the effect of smoking on the lung.

OESTROGENS IN OSTEOPOROSIS

It is only during the last decade that osteoporosis has been generally recognized as a fairly common condition. Much of our knowledge about it has come from the work of Fuller Albright and his associates on bone metabolism.[1 2] There are two chief varieties of widespread loss of density of bones. In the first, osteomalacia, there is failure to deposit calcium salts in the organic matrix of bone. This arises whenever

the calcium ions or phosphate ions are at too low a level in the serum to permit the osteoblasts to precipitate the calcium-phosphate-carbonate complex. Though rigid, bone is far from being in a fixed, immutable state but is in constant flux with resorption and renewal going on continuously. Failure of deposition of calcium salts therefore leads to weakness of the bones of the type which is manifested as rickets in children and osteomalacia in adults. The weakening of the bones increases the stresses and strains on the bony structure, and this stimulates the osteoblasts to greater activity, which is reflected by a rise in the serum alkaline phosphatase.

In the second variety of loss of bone density, osteoporosis, there is no defect in the process of calcification, but the organic matrix of the bones becomes deficient. Local osteoporosis occurs through disuse atrophy, as in prolonged splinting or in immobility due to painful, diseased joints. Generalized osteoporosis occurs in several groups of patients: in women after the menopause, in old people of both sexes, in various endocrine disorders (hypopituitarism, acromegaly, eunuchoidism, Cushing's syndrome, and ovarian agenesis), and sometimes as an "idiopathic" type in young subjects. There is also nowadays a considerable iatrogenic group due to the use of cortisone and its analogues in large doses. The corticosteroids are catabolic agents which produce a negative nitrogen balance, so it is not surprising that osteoporosis is likely to complicate their prolonged administration in high doses. The biochemical findings in the blood are usually entirely normal. The spine and pelvis are most affected, the patient commonly feeling pain in the back. Radiographs show poor density of the vertebral bodies and expansion of the intervertebral disks, which bulge into the vertebral body, pushing the bony end-plates in front of them, so that the appearance is that of a "fish-spine." In due course, one or more vertebral bodies are likely to collapse. The long bones may also be affected, and this possibly accounts for the way in which old people are prone to fracture their bones with slight trauma, especially the neck of the femur.

In most cases of post-menopausal and senile osteoporosis a deficiency of sex hormones appears to be one of the main causes of the condition. Both androgens and oestrogens have been tried singly or in combination in treatment, and also as a preventive measure when cortisone and allied steroids are being given for long periods. Both have an anabolic action on protein, though the action is possibly more convincing with the androgens. The first evidence from balance studies that oestrogens and androgens improved the calcium balance of patients with osteoporosis was presented by Albright and his colleagues in 1940.[3] P. H. Henneman and S. Wallach[4] have now published a review of the results of prolonged oestrogen and androgen therapy in post-menopausal and senile osteoporosis among the patients treated by Albright during the past 20 years. In addition to hormone therapy, a nutritious diet containing ample protein is necessary to encourage good formation of bone matrix. Immobilization must be avoided, because, though a spinal brace will relieve the pain of osteoporosis, it will only encourage the progress of the disease. Calcium and vitamin D are not required above the amounts found in a good diet. Regular measurements of the height of the subject provide a simple objective test of the efficacy of treatment, for, when it is unchecked, osteoporosis leads to a progressive diminution of stature. Henneman and Wallach report that oestrogen therapy increases calcium retention in post-menopausal women and testosterone causes increased calcium retention in senile men. They present evidence that combined androgen and oestrogen therapy is more effective than either alone in the senile man, whereas the addition of androgens makes little difference to the beneficial effect of oestrogen therapy in post-menopausal women. This last finding is of consequence because the use of androgens in women is apt to be accompanied by undesirable side-effects, such as deepening of the voice, facial hirsuties, enlargement of the clitoris, and excessive libido, though a number of androgen-like substances are now being developed in which androgen activity is slight while anabolic activity is high.[5] Conversely, oestrogens produce undesirable effects in men, such as gynaecomastia, impotence, and testicular atrophy, so their use is best reserved only for the most severe cases in men. One objection to the long-continued administration of oestrogens to women has been the fear that it might induce carcinoma of the sex organs and breasts. It is therefore of importance that Henneman and Wallach are able to report that among 200 women treated with oestrogens for from one to twenty years, with a total of 1,100 patient-years of follow-up, only four instances of genital carcinoma occurred. They comment: "Since these patients were all in the 'cancer age group,' this appears to be a low incidence of genital cancer and does not justify the fear that prolonged oestrogen therapy may be carcinogenic."

[1] Albright, F., Burnett, C. H., Parson, W., Reifenstein, E. C., and Roos, A., *Medicine (Baltimore)*, 1946, **25**, 399.
[2] Albright, F., and Reifenstein, E. C., *The Parathyroid Glands and Metabolic Bone Disease: Selected Studies*, 1948, Williams and Wilkins, Baltimore.
[3] Albright, F., Bloomberg, E., and Smith, P. H., *Trans. Ass. Amer. Phys.*, 1940, **55**, 298.
[4] Henneman, P. H., and Wallach, S., *Arch. intern. Med.*, 1957, **100**, 715.
[5] Gordan, G. S., ibid., 1957, **100**, 744.

POLIOMYELITIS VACCINE

When the Government decided to import Salk vaccine from N. America last September[1] there was good reason for hoping that all those in the priority classes registered for immunization would have received their injections by the end of next June. Admittedly the Government's decision was tardy; four months before it was taken we were asking what justification there was for refusing to import the vaccine.[2] But, once having changed its mind, the Government quite rightly enlarged the immunization scheme and offered vaccination to all children under 15 and to expectant mothers. Before this only children under 10 had been offered vaccination. Last autumn, with British vaccine coming from two British pharmaceutical companies and with the promise of 5,000 litres of Salk vaccine from companies in Canada and the U.S.A., it looked as though the Minister of Health's troubles were nearly over, and that all those registered—about 6,000,000—would be safely vaccinated before poliomyelitis became prevalent this summer. By the end of February, 1958, over 2,000,000 children had received the full course of two injections.

Unfortunately, as the Minister explained in Parliament last week,[3] the supply of vaccine to local health authorities has been seriously interrupted during the last few weeks. For one reason or another each of the four companies supplying the vaccine—two in Britain, one in Canada, and one in the U.S.A.—have had difficulty in filling their orders: monkeys used for testing the vaccine have fallen ill, live virus was found in one batch, another batch failed to pass antigenic potency tests, and unexpected domestic demand apparently reduced the amount of Canadian vaccine available for Britain. This is an unhappy chapter of accidents for which it is foolish to blame the Minister of Health, Mr. Derek Walker-Smith; where he is at fault is for not having uttered a cautionary note about supplies of a substance so fickle in its behaviour during production. He has taken energetic steps to make good the deficiency, and, as he told the House of Commons this week, further supplies of Salk vaccine are on their way from Canada and the U.S.A.

Meanwhile local health authorities are faced with a very big task, for it is their responsibility, when the vaccine is available, to see that those who have registered in their area are vaccinated. According to a statement issued by the Ministry of Health last week 3,000,000 people (mainly children) were awaiting vaccination at the end of February (the last date for which figures were available), and a further 650,000 had had one injection and were awaiting another. In other words, 6½ million injections had still to be given in the course of four months. One thousand doctors working a five-day week and giving 75 injections a day would be just about completing this task by June 30 if they had started on March 1. Even by taking their medical officers off routine work such as school medical inspection and by using to the full all the help that general practitioners can give them, local health authorities will be hard pressed to complete this work in time, even if there is no further interruption in the supply of vaccine. At the same time it is well to recall that poliomyelitis, compared, for example, with tuberculosis, is not a large public health problem in this country, that the greater part of those infected do not suffer any form of paralysis, and that of those who do have some form of paralysis some three-quarters make a good functional recovery. Tuberculosis, though now more easily controlled, affects a vastly greater number of people; but as the results of the disease are invisible and undramatic the public interest in it is not so easy to arouse. And, if we look at another disease which attacks the nervous system, it is of some interest to note that in the five-year period 1952–6 there were 1,234 deaths from meningococcal infection as compared with 1,062 from poliomyelitis.

It is highly regrettable that poliomyelitis has in the past been allowed to become a political problem, causing alarm to the public and creating a false picture of the disease in the community. It is to be hoped that any decision on re-testing in this country imported Salk vaccine will not be influenced by any political considerations, but be made as a result of the best scientific advice available. If our experts are completely satisfied with tests made on, say, firm X's vaccine in the U.S.A., and conditions of transit are as good as one would expect them to be, then re-testing might be considered to be a waste of time when the vaccine arrives in Britain. There can be no doubt that experts in the U.S.A. and Canada are just as capable as we are of making efficient tests. If our experts are satisfied that the tests are stringent by our standards, then the Minister of Health will have no difficulty in coming to a correct decision.

[1] *Brit. med. J.*, 1957, **2**, 651 and 688.
[2] Ibid., 1958, **1**, 1229.
[3] Ibid., 1958, **1**, 1010.

HYPERTENSION AFTER X-IRRADIATION OF THE KIDNEYS

Until five years ago the kidney was regarded as a relatively radio-resistant organ, despite the evidence from animal experiments[1–4] and occasional references to effects from renal irradiation in man.[5–8] In 1953, R. W. Luxton,[9] in a notable paper, made a detailed analysis of 27 cases of "radiation nephritis," describing four main syndromes—acute and chronic radiation

nephritis, benign hypertension, and late malignant hypertension. He described the latent period of 6–12 months between the time of *x*-ray therapy and the onset of signs and symptoms, and emphasized the curious disparity in degree and in timing between hypertension and renal failure, but could offer no explanation thereof. Recently Professor C. Wilson and his co-workers[10] at the London Hospital have reported that in some patients who developed hypertension after abdominal irradiation the histological abnormality found in the kidneys was indistinguishable from that of malignant *essential* hypertension. In an attempt to clarify the relationship of the hypertension to renal structural changes they made a series of carefully planned and ingeniously devised experiments on rats, their technique ensuring that what they observed was the outcome of irradiation of kidney tissue only. Some experiments entailed the drawing out on to the rat's flank of one or both kidneys (exteriorization) prior to irradiation; in others the kidneys were irradiated *in situ*. The experiments showed that irradiation of both exteriorized kidneys in rats caused hypertension after a latent period corresponding with that in man, and similar histological changes of renal sclerosis. Irradiation of one kidney only (after its exteriorization) causes sclerosis of that kidney and systemic hypertension, but the non-irradiated kidney, which enlarges, shows merely the histological changes due to systemic hypertension. These changes (fibrinoid necrosis of arterioles and glomeruli, focal tubular dilatation and hyaline droplet degeneration of the tubular epithelium) are identical with those seen in a kidney after the renal artery of its opposite number has been constricted. There is no evidence that the hypertension which follows irradiation is due to constriction of the kidney by capsular fibrosis or of the renal artery by hilar fibrosis.

Irradiation of both kidneys *in situ* in the rat caused hypertension and renal structural changes similar to those arising under comparable conditions in man, in whom the clinical syndrome of malignant hypertension may arise 9 to 12 months after abdominal radiotherapy. The workers at the London Hospital made the interesting discovery that if the rat's kidney is excised at the onset of hypertension it may appear histologically normal. This production of renal hypertension in the rat, without obstructing the renal circulation and without manifest renal damage, is important because of the light it may shed on the causation of essential hypertension in man. Wilson and his colleagues concluded that renal irradiation in the rat has two distinct and independent biological effects—interstitial fibrosis and hypertension—and these two effects have different time relations and may develop together or separately. Their experimental work provides a clear explanation of Luxton's clinical observations in man and of H. Russell's[11] pathological findings in these patients, for both the clinical and histological features of human radiation nephritis are the outcome of hypertension and renal irradiation sclerosis combined in varying degrees.

Malignant hypertension is an unpleasantly frequent sequel of renal irradiation. The observations of Wilson and his colleagues suggest that *x*-radiation makes the arterial structures of the kidney unduly sensitive to hypertension—as if irradiation sets the whole mechanism of malignant hypertension on a hair trigger. Malignant hypertension is seen in three circumstances after therapeutic *x*-radiation of the abdomen in man. It may appear as a consequence of acute radiation nephritis 9 to 12 months after irradiation, the kidneys then being of normal size. Two to ten years after irradiation, "late" malignant hypertension may develop, again the kidneys being of essentially normal dimensions. Lastly, if one kidney only has been heavily irradiated (as occurs in the treatment of a malignant mass in its close proximity, or when, owing to its malposition, one kidney receives an exceptional dose during prophylactic irradiation of the abdomen after orchidectomy for seminoma) that kidney may undergo extreme sclerosis and malignant hypertension result from the unilateral renal lesion. As emphasized by W. M. Levitt and S. Oram,[12] this variety is important to distinguish, for it can be relieved by unilateral nephrectomy. Late malignant hypertension unassociated with unilateral renal contraction responds to hypotensive drugs, the use of which must not be delayed, however, for the condition may progress with exceptional speed.

[1] Schulz, O. E., and Hoffmann, R. St., *Dtsch. Z. Chir.*, 1905, **79**, 350.
[2] Hartman, F. W., Bolliger, A., and Doub, H. P., *Amer. J. med. Sci.*, 1926, **172**, 487.
[3] O'Hare, J. P., *et al.*, *Boston med. surg. J.*, 1926, **194**, 43.
[4] Bennett, L. R., *et al.*, *Radiology*, 1953, **61**, 411.
[5] Warthin, A. S., *Amer. J. med. Sci.*, 1907, **133**, 736.
[6] Dean, A. L., and Abels, J. C., *J. Urol.*, 1944, **52**, 497.
[7] Zuelzer, W. W., Palmer, H. D., and Newton, W. A., Jr., *Amer. J. Path.*, 1950, **26**, 1019.
[8] Doub, H. P., Bolliger, A., and Hartman, F. W., *Radiology*, 1927, **8**, 142.
[9] Luxton, R. W., *Quart. J. Med.*, 1953, **22**, 215.
[10] Wilson, C., Ledingham, J. M., and Cohen, M., *Lancet*, 1958, **1**, 9.
[11] Russell, H., *Edinb. med. J.*, 1953, **60**, 474.
[12] Levitt, W. M., and Oram, S., *Brit. med. J.*, 1956, **2**, 910.

SECRETION OF CORTISOL

It is now accepted that one of the major products of the human adrenal cortex is cortisol (hydrocortisone). A knowledge of the normal rate of production of this hormone is obviously desirable in order that the connexion between adrenal activity and various pathological conditions may be clearly established. A number of estimates of the daily secretion of cortisol in man have been made, but these are based largely on indirect evidence and are open to criticism on other grounds. In spite of this it is interesting to find that most workers report an output within the relatively narrow range of 5–50 mg. daily, with a mean figure around 20 mg. This agrees well with the observation that the Addisonian or adrenalectomized patient requires about 12.5–25 mg. of cortisone a day, although it is possible that the absence of other steroids may influence the amount of replacement therapy needed. Estimates based on the excretion of steroid metabolites in response to a given dose of cortisol yield somewhat similar figures, but it may be unwise to assume that these necessarily reflect intrinsic adrenal activity. A more direct method would be to determine the amount of cortisol in blood from the adrenal vein, a technique that has been much used in the experimental animal. It is possible, for example, to insert a cardiac catheter into the human renal or adrenal vein[1]; blood

[1] Masoni, A., *Acta med. scand.*, 1957, **159**, 225.
[2] Halberg, F., *J.-Lancet*, 1953, **73**, 20.

has been obtained by this means and also at operation in a few patients. Apart from the obvious objection that the stress of the procedure may give rise to abnormally high values, there is the added disadvantage that the results of a short period of observation must be extrapolated to obtain a measure of the total daily output. In view of the known diurnal variation in adrenal cortical activity, which is at its maximum in the early morning and gradually falls during the day,[2] the final figure will almost certainly be too high.

The need for a simple method of estimating daily cortisol production has led Dr. C. L. Cope and Miss E. Black to explore the possibility of using ^{14}C-labelled cortisol, and we publish their results at p. 1020 of this week's *Journal*. The principle is similar to that used in other isotope techniques. A minute amount of the labelled compound is introduced into the body (the oral route appears to be satisfactory), and this becomes diluted by endogenously produced cortisol. Since it is metabolized in the same manner as the natural steroid, the radioactivity of the end-products—in this case certain tetrahydro compounds—can be used as an indicator of the degree of dilution. All that is needed is a 24-hour collection of urine in which to measure the specific activity of the metabolites. This can then be compared with the original activity, and, with the initial dose known, the daily production of endogenous cortisol can be readily calculated. By this means Cope and Black have found an average output of 13–14 mg. of cortisol in normal subjects, which probably represents as nearly basal levels as it is possible to achieve. It is significant that the figures are lower than those obtained by any other method. The present technique has the great advantage that it is easy to carry out in ill patients, and the authors have already investigated adrenal activity in a variety of diseases. Such a simple and practical method should commend itself to those interested in adrenal function.

MECHANISM OF SUCKLING

Following on their cineradiographic study of bottle-feeding,[3] which was discussed in these columns recently,[4] G. M. Ardran, F. H. Kemp, and J. Lind proceeded with similar investigations during breast-feeding.[5] They showed, by cineradiography, that during suckling the mother's nipple elongates and the end approximates to the junction of the infant's hard and soft palates, the neck of the teat being held between the upper gum and the tip of the tongue. By comparison with an artificial teat it appeared that the mother's nipple formed only the bulbous end, the remainder of the "teat" being composed of stretched breast tissue surrounding the attachment of the nipple. The mechanism of suckling was identical to that seen in bottle feeding, as was swallowing.

The action of the infant's tongue and lips in the process of suckling has for long been debated. It is generally held that the tongue remains relatively immobile—at least to the extent that tongue-tie cannot interfere with feeding. The part played by the lips is probably passive, though it has been suggested that they grasp the breast and may actively be concerned in the expression of milk, but E. Gwynne-Evans[6] was able to show that they did not always maintain close contact with the areola. Ardran and his colleagues felt that their most likely function was to compress the breast and so increase the pressure on the lacteal sinuses. The question of active suction remains to be solved; it has not yet been possible to visualize the subareolar ducts (lacteal sinuses or cisterns) during the process of suckling.

[3] Ardran, G. M., Kemp, F. H., and Lind, J., *Brit. J. Radiol.*, 1958, **31**, 11.
[4] *Brit. med. J.*, 1958, **1**, 392.
[5] Ardran, G. M., Kemp, F. H., and Lind, J., *Brit. J. Radiol.*, 1958, **31**, 156.
[6] Gwynne-Evans, E., *Brit. dent. J.*, 1951, **91**, 135.

"TO-DAY'S DRUGS"

About thirty drugs are advertised in this issue of the *Journal*. Most of them are of recent introduction and highly potent, a few are old friends, and some are mixtures of old and new. Next week there will be fresh names among the advertisements, and so on throughout the year. Even the expert finds it exceedingly difficult, if not impossible, to sift all the evidence and firmly to assign many of to-day's drugs to their place in the treatment of disease. How much more difficult, then, is it for the physician in the hurly-burly of clinical practice to make up his mind when to try a new drug, especially if it means abandoning, even temporarily, an older and trusted remedy with whose action he is entirely familiar?

As a concise guide through the modern therapeutic maze we hope to publish at intervals authoritative short notes giving practical guidance on new drugs and on older drugs appearing in new forms. They will appraise some of the recently issued proprietary and non-proprietary remedies, so that clinicians may have an up-to-date, informed, and expert commentary on them. The first of this series appears at p. 1061 under the title of "To-day's Drugs."

POSTGRADUATE CONFERENCE AT R.C.P.

The first of what is hoped to be a series of postgraduate conferences is to be held on July 25 and 26 at the Royal College of Physicians of London. Full details are given in an advertisement elsewhere in this issue. The conference will be on "Anaemia and the Alimentary Tract," and is being arranged principally for Fellows and Members of the College who are consultants in medicine or pathology. Coeliac disease, adult steatorrhoea, unexplained alimentary bleeding in anaemia, and oesophageal lesions are some of the subjects to be discussed. The papers will be short so as to allow plenty of time for discussion. The decision of the College under its President, Professor Robert Platt, to express in this way its concern with the academic and educational functions of the College will be widely and warmly welcomed.

SYMPOSIUM ON CLINICAL TRIALS

[FROM A SPECIAL CORRESPONDENT]

What Professor R. CRUICKSHANK described as "this essentially British method for the assessment of drugs" was the subject of a day's symposium last Friday at the Royal Society of Medicine. Surprisingly, it was said to be the first held in Great Britain on the subject, and the organizers, Messrs. Pfizer Ltd., are to be congratulated on their initiative. Sir CHARLES DODDS, F.R.S., the chairman, expressed the opinion of many medical as well as pharmaceutical men when he referred in his opening remarks to clinical testing as "the most burning question in medical therapeutics." For the human being as the final test object, he continued, remained as remote as he was fifty years ago. As other speakers were to do, he emphasized the difficulties of finding clinicians with sufficient time and training to carry out the work.

Ethics

Dr. J. G. SCADDING, of the Brompton Hospital, gave the first address, and immediately struck a note that was to echo throughout the day—namely, the ethics of clinical trials. A presupposition, he said, was that full animal experiments had been carried out, and sometimes experiments on a few human volunteers; a pilot trial might follow, and then a controlled trial. Discussion in the course of the day showed that most speakers thought this procedure was sound in general, though such disagreement as there was centred on the nature of the pilot trial or preliminary clinical observations. The fact that these could not, owing to their design (or lack of it) give a decisive answer is a feature that the more rigorous mathematicians found unattractive but the more experienced clinicians acceptable within its limits. As Professor R. A. KNOX, of Guy's Hospital, suggested, this is a subject that is worth defining clearly and debating on a future occasion. In experimental work the borderline between a preliminary and a premature conclusion can cause strong language to flow.

The advantages of using in a clinical trial all the early supplies of a new drug were apparent, said Dr. Scadding, and physicians were chary of carrying out a trial with a drug they had evidence for believing was more beneficial than its alternatives. He pointed out that in some circumstances ethics would always make a therapeutic trial impermissible. For example, in the treatment of early operable cancer of the bronchus by surgery or radiotherapy a presumption existed in surgeons' minds that operation was the more beneficial.

Controls and Conscience

Professor J. W. CROFTON, of Edinburgh, the next speaker, after saying that the control group was in many respects the safest one to belong to, pointed out that in some situations no control group was required. This might be when testing the treatment of a highly fatal acute disease, such as tuberculous meningitis with streptomycin, or when testing a new drug with consistently dramatic results, such as chloramphenicol in scrub typhus. But there was an area of doubt, and here, he declared, it was unethical *not* to have a clinical trial. He stressed too, as did other speakers, that the physician taking part in the trial—which entails his adhering closely to a protocol of treatment—must have a "conscience clause" so that he can give his patient the best possible treatment regardless, if necessary, of the trial's requirements. It was important, he said, to define "the best treatment previously available," so that the control group should have it.

A digression followed when Professor S. J. HARTFALL, of Leeds, asked what was really happening in the 20% or 30% or so of controls who reacted to a placebo in so many trials. And Sir CHARLES DODDS inquired disarmingly whether lactose was a new wonder-drug. Dr. SCADDING thought the improvement in the control groups was largely due to the natural course of the disease, except when it was obviously psychological, as in asthma.

Measures and Errors

Criteria for measurement in acute diseases and chronic diseases were the subject of the next two papers, and the work of Dr. C. M. Fletcher, of the Postgraduate Medical School, on observer error in the reading of *x*-ray films was mentioned with appreciation. Professor R. CRUICKSHANK, of Edinburgh, pointed out that objective measurements of clinical progress, though often preferable to subjective, were subject to error which might be considerable. His illustration by means of neat graphs of the measurements used in various trials—pyrexia, bacterial counts, and so on—gave added point to the remark of the next speaker, Dr. O. SAVAGE, of the Arthur Stanley Institute for Rheumatic Diseases of the Middlesex Hospital, that assessing the value of a drug was far more difficult in chronic than in acute disease. Dr. Savage discussed particularly rheumatoid arthritis, and said that no satisfactory method of assessing pain had yet been devised; they had also given up tests of joint movement as too unreliable. Tenderness and grip provided the best objective tests in this disease. At least four methods were in current use, he said, for measuring disability in rheumatoid arthritis, and they were all largely subjective.

The only statistician to speak, Dr. I. SUTHERLAND, of the Medical Research Council, also expressed a preference for objective measurements. If they had to be supplemented by subjective measurements, he said, then these must be made in ignorance of what treatment the patient was receiving. The essentials of a comparative trial (he preferred this epithet to "controlled") Dr. Sutherland summarized as: (1) definition of ethical aims; (2) selection of a population; (3) recruitment of enough subjects; and (4) random allocation to a series. The sequential approach, which allows the trial to come to an end on the nature of the data instead of a prior decision of the investigator, might find more use, he thought, in testing treatment of the acute diseases when it becomes better known.

Dangers of Enthusiasm

The results of treatment with many familiar substances are still not precisely known. Dr. DUDLEY HART, of the Westminster Hospital, pointed to gold salts as an example. And Dr. MAURICE DAVIDSON, London, expressed a similar thought when he said that the release of drugs for general use had sometimes been over-hasty. Dr. Hart dwelt on the dangers of enthusiasm in the staff concerned in a therapeutic trial and showed how a "revivalist" atmosphere surrounding the introduction of a new method of treating rheumatoid arthritis could not merely upset the recording of observations and the deductions to be made from them, but could lead to the production of entirely misleading data by patients whose reactions to treatment sprang from a strong expectation of cure. Among the rules he set out for the careful control of a trial were: "Be disinterested," and "Consult a statistician beforehand." But from what several speakers said it seemed that the term "statistician," when used appreciatively, was more or less restricted to those sensible people who had been trained or were working at the London School of Hygiene and Tropical Medicine.

Summing up what he thought should be the ideal way of introducing a new remedy, Dr. Davidson said it had three phases. The experimentalist, after determining its effects on animals, submitted it to the M.R.C. or some such body; this would arrange to test it clinically; then it would go to senior physicians in the larger hospitals. After that it was released for general prescription.

Paying for Trials

Finally, a thought-provoking contribution came from Professor A. KEKWICK, of the Middlesex Hospital, on the reasons why pharmaceutical houses promote clinical trials and how they pay for them to be carried out. He divided the trials into three categories. In the first, the trial was intended to provide the firm with information about a new drug. And if the firm wanted information it should pay for

it, but the fee should be for that and not for publication of results. Secondly, there was the "consumer trial" on a variation of an already accepted remedy. No conclusive result was likely from such a trial. Pharmaceutical houses sometimes asked general practitioners to report on a drug for a fee. But there was a complication in that the G.P.'s first duty was to his patient, and it would be undesirable for him if he got a reputation locally for trying out new drugs. Professor Kekwick thought such consumer trials should not be done for a fee except through some body such as the College of General Practitioners. Thirdly, there were "promotional trials." Here a pharmaceutical house took a remedy on which a good deal of work had been done, farmed it out to well-known people, and wanted publicity by means of publications on it. He thought this type of "trial" should finish altogether; he personally did not believe it was good publicity until representatives of pharmaceutical houses had told him that it was. Pharmaceutical houses, he emphasized, must state exactly why they wanted a trial.

In the subsequent discussion conflicting views were expressed on the payment of the investigators carrying out trials, though the general opinion seemed to be that work done should be paid for in some way. The dangers of a university department becoming largely dependent for finance on a particular drug firm, as sometimes happens abroad, were stressed by one speaker, and of eminent men pushing new and perhaps dangerous drugs by another. There was some disagreement too on whether student volunteers should be paid.

But on at least one point every speaker seemed to be unanimous, and that was that clinical trials depend for their success on the random allocation of patients to treatment categories, preferably by means of random numbers. How these are to be identified or defined was, perhaps fortunately in the time available, not discussed. So long as the investigator can go out and buy a book of them and get satisfactory results with it, their precise (if elusive) nature remains a topic for the common-room rather than the conference.

ASSESSMENT OF DRUG ACTION

MEASUREMENT IN MAN

[FROM A SPECIAL CORRESPONDENT]

A symposium on "Quantitative Methods in Human Pharmacology and Therapeutics" was held in the Wellcome Auditorium, London, on March 24 and 25. It was arranged by the Co-ordinating Committee for Symposia on Drug Action, of the Biological Council, and was supported by the British Pharmacological Society, the Royal Society of Medicine, the Physiological Society, and the Biometric and Nutrition Societies.

The Case for Exactitude

Opening the meeting, Sir CHARLES HARINGTON, F.R.S., said that those like himself who hankered for the time when research workers could be satisfied with qualitative observations must firmly repress their wishes. Quantitative studies were vital to the advance of therapeutics as well as in the laboratory.

Professor J. H. GADDUM, F.R.S., confirmed this view. The advance of drug therapy was only in part due to the provision of new drugs, he said. Without exact measurement of their effects further new drugs could not be made. Even where cures were not available, as in the common cold, we could at least show that proposed remedies were less effective than some people thought. He hoped no one would fail to attend the session on statistics because they thought it might be too difficult for them to understand: doctors did not have to understand statistics; what was important was that they should know what statistics could do for them and what it could not. Dr. A. C. DORNHORST then described quantitative methods for measuring drug effects on flows and pressures in man, Drs. R. V. PITT-RIVERS, F.R.S., and W. R. TROTTER discussed problems of the evaluation of the effects of thyroid hormones, Dr. E. ZAIMIS the estimation of neuromuscular block, and Dr. E. N. ROWLANDS the effect of drugs on the gastro-intestinal tract.

The discussion was opened by Dr. HARRY GOLD, who gave the conclusions he had reached after 35 years of making exact measurements of drug effects in man. He spoke especially of the evaluation of drugs in angina pectoris, of digitalis and diuretics. He described how his group of workers at Cornell University came to develop the "double-blind" technique in which neither patient nor doctor knew what treatment the patient was having, as a result of experience showing that neither doctor nor patient was free from unconscious bias when judgments were subjective, unless they were ignorant of the nature of the treatment. Doctors were still sometimes unwilling, he said, to accept that they are subject to bias just like their patients.

Subjective Effects

The second session was principally on the measurement of subjective states. Professor C. A. KEELE described how pain could be measured in man and how analgesic drugs could be compared. The best way was to rely on subjective assessments by the victim rather than to attempt to measure the physical changes which accompany pain—for example, sweating, change in pulse rate, wincing. These were too variable. He discussed the production of experimental pain in man and proposed a scheme for expressing analgesic power and incidence of side-effects as one number which would enable the easy comparison of therapeutic suitability of drugs. This proposal proved to be controversial.

Dr. P. SAINSBURY described how, by electromyography, he measured muscle tone and involuntary movements, fidgeting, gestures, in anxious patients, and how the effect of drugs on these physical accompaniments of anxiety could be assessed.

Dr. H. STEINBERG discussed the measurement of intellectual performance, reasoning, memory, perception, vigilance, and how drug action could be evaluated. The effect of drugs on performance could be either on incentive or on the actual ability to do the job. It was important to distinguish between the two. Drug responses could vary according to whether a subject knew if he was doing well or badly in a test. Small amounts of anxiety acted as an incentive, and it was probably important that this should not be suppressed by drugs or achievement might be prevented. Fortunately this problem was not socially urgent, as drugs were relatively ineffective in allaying anxiety without producing other undesirable effects. Professor L. GOLDBERG described how the effects of drugs on ability to maintain steady posture could be measured. Dr. H. K. BEECHER described the measurement of subjective states.

The third session was opened by Dr. W. G. COCHRAN, who described the newer statistical techniques available for biological experiments, such as Latin squares, randomized blocks, and sequential analysis, and examples of the practical application of these methods were given by Drs. H. O. SCHILD, J. G. DARE, J. L. MONGAR, and W. Z. BILLEWICZ. The evaluation of data ranged by pluses and minuses, and the accuracy which such a subjective assessment could achieve was discussed by Dr. C. C. SPICER.

Human Experimentation

The final session was opened by Professor A. BRADFORD HILL, F.R.S., who said that clinicians had now come to accept the value of statistical techniques as an essential part of finding out whether a treatment was really effective, even when they did not understand how the results were handled by the statistician. This was an important advance.

Drs. A. SPINKS and G. E. PAGET described how to assess the toxicity of a compound in animals before its trial in man. The tests used were admittedly unsatisfactory, but there was no alternative. Professor W. A. BAIN described how pilot clinical trials could be designed to give maximum information with minimal risk in the case of new drugs, and Dr. W. R. S. DOLL reviewed the design of larger clinical

trials. He discussed the type of controls needed and the allocation to treatment groups, giving examples illustrating the problems involved.

Dr. T. F. Fox concluded the symposium with his views on the ethics of human experimentation. He said that patients must be able to rely on doctors doing their best for them, uninfluenced by the requirements of science. On the other hand, the patient must realize that it was in his interests that science should advance without serious impediment. A conflict could develop here. When there was any difficulty in obtaining not only the patient's consent but his valid consent to an experiment, then the doctor should call in another doctor to help the patient, with his technical knowledge, to decide whether or not to undergo the experiment. In the discussion that followed the opinion was expressed that this was not only impracticable but undesirable, as intervening between the physician and his patient on the occasions when the physician later became experimenter. No adequate alternative solution was proposed, but it was felt that the doctor's conscience alone, coupled with criticism by his peers in research and by editors of journals who published his work, should provide adequate safeguards.

The proceedings of the symposium will be published by the Pergamon Press, London.

OPHTHALMOLOGICAL SOCIETY OF THE UNITED KINGDOM

[FROM A SPECIAL CORRESPONDENT]

The 78th annual congress of the Ophthalmological Society of the United Kingdom was held at the University College of South Wales and Monmouthshire, Cardiff, on April 17, 18, and 19. Mr. J. J. HEALY, the Society's president, was in the chair.

On the first day there was a discussion on the complications and treatment of the hypermature cataract, a number of scientific papers, the business meeting, and the annual dinner; on the last day there were more scientific papers. This report is confined to the proceedings on the second day, when the main topics were the ocular lesions of toxoplasmosis and precancerous melanosis.

Ocular Toxoplasmosis

Professor C. P. BEATTIE, of Sheffield, opened the symposium on toxoplasmosis. The *Toxoplasma*, he said, had a singularly wide zoological and geographical distribution, with human infection varying from 5% in Iceland to 70% in Tahiti. In Britain about one-quarter to one-half of the adult population had been infected, although we were still ignorant of the usual route of spread. In the congenital form, where at least transmission was definitely known to be via the placenta, a chorioretinitis was the most constant manifestation, and indeed most toxoplasmic chorioretinitis was of congenital origin. Acquired infections were usually innocuous, featuring a lymphadenopathy resembling glandular fever.

In congenital cases serological studies in adults were not very helpful, as usually by then the levels of toxoplasmic antibodies had fallen to around those in the general population due to latent infection; at best one could only infer the probability of a toxoplasmic origin in any given case of chorioretinitis. In young children, however, the diagnosis was relatively easy, for in the rare cases where antibodies were present they were also generally of high titre. Dr. J. K. A. BEVERLEY, also of Sheffield, said that even in highly immune animals the parasite could and did multiply. He summarized the results of chemotherapy in acute experimental infections, and then discussed the hypersensitivity reactions and how these could best be controlled.

Mr. E. S. PERKINS, reader in ophthalmology at the Institute of Opthalmology, London, considered the more specifically ophthalmological aspects of toxoplasmic infection. He emphasized there was now good statistical, therapeutic, and pathological evidence that toxoplasmosis caused uveitis in adults as well as the congenital chorioretinitis. Unfortunately, serological evidence of infection with toxoplasmosis was common in normal adults, and, while a negative dye test probably excluded toxoplasmosis, a positive test did not prove the aetiology of an individual case of uveitis. Possibly some cases of anterior uveitis were due to toxoplasmosis, but at present these cases could not be recognized clinically.

Cases of posterior uveitis, however, had a high percentage of positive dye tests—particularly the acute and subacute groups. In the 106 cases of posterior uveitis from a total series of 653 cases of uveitis of all types, 82% of the acute and subacute posterior groups had positive dye tests (over 1:4) compared with some 50% in all the other types of uveitis; and as the patients in these groups were younger than the series as a whole their higher incidence of positive tests was even more surprising. These cases were characterized by focal patches of chorioretinitis near the main retinal vessels and macula or at the margin of the optic disk. The active lesion was often at the edge of an old scar, which suggested that most of these lesions were recurrences of congenital infections. However, in 19 cases with a positive dye test (including five with a lesion at the macula) there was no evidence of a previous lesion, and, although it was difficult to prove that all or indeed any of them were due to toxoplasmosis, probably some were; they might have followed infection acquired after birth, perhaps even in adult life.

Disseminated choroiditis was not associated with positive dye tests and was unlikely to be due to toxoplasmosis, and the same was true of retinal vasculitis.

Precancerous Melanosis

The discussion on precancerous melanosis of the conjunctiva was opened by the president, Mr. J. J. HEALY, of Llanelly. He described three cases he had recently seen illustrating different aspects of this condition; one had progressed to frank cancer. He was followed by Dr. M. LEDERMAN (London), who discussed the role of radiotherapy in cancerous and precancerous melanosis. His results of treatment at the Royal Marsden Hospital, and his views on the indications for such treatment, were at variance with those enunciated recently by Mr. A. B. Reese. Twelve out of 14 patients with cancerous melanosis had been treated by radiotherapy; two of them died of metastases, but the remainder had survived for intervals of up to seven years. From this Dr. Lederman concluded that at any rate some of these tumours were radiosensitive. He had tried various methods of irradiation, including beta radiation from radium or radioactive strontium, and gamma radiation from radon seeds and radioactive tantalum wire. Some of those treated with the tantalum wire had had unduly severe reactions, so his preference was for beta radiation because of its minimal complications.

Mr. FREDERICK RIDLEY (London) continued the discussion by describing in detail the special contact shells used in this form of therapy, and finally Dr. A. L. WELLS, of Llanelly, considered the question of whether precancerous melanosis is a specific entity, comparing its pathological features with similar lesions in cutaneous squamous epithelioma generally.

Visual Loss after Pituitary Irradiation

Dr. R. W. HARRINGTON, of Glasgow, discussed the damage to the chiasma and hypothalamus that might follow the use of radioactive implants in the pituitary fossa in cases of inoperable hormone-dependent cancer. He described the difficulties in inserting the implants accurately, preferring seeds containing the short-acting beta-emitter yttrium-90 to those with radon, a gamma-emitter. He then illustrated the field changes found in 12 out of a total of 63 patients examined.

Mr. ARTHUR LISTER (London) presented his observations on the results of perforating cyclodiathermy. He had found it more effective than surface cyclodiathermy, especially in the treatment of chronic glaucoma in the elderly, although he had some doubt about the permanence of its effect.

Mr. A. G. CROSS (London) discussed the treatment of chronic uveitis. It had been revolutionized by the adreno-

cortical hormones, which readily damped down the acute cases till they had run their usual short and predetermined course. He described in detail the various methods of dealing with the more serious problems of chronic uveitis where the outlook, although much better than it was ten years ago, was still grave, blindness often resulting.

Mrs. DOROTHY MILLER (London) reported a case of anorexia nervosa in a young woman which was followed by the development of subcapsular cataracts. These were thought to be probably nutritional in origin. Finally, Dr. JOHN MCARTHUR (London) demonstrated a microscope that he had developed for medical and research use. It was no bigger than a miniature camera.

HORMONES AND ATHEROSCLEROSIS

MEETING IN UTAH

[FROM A SPECIAL CORRESPONDENT]

A conference on "Hormones and Atherosclerosis" took place at Brighton, Utah, from March 11 to 14, under the general chairmanship of Dr. GREGORY PINCUS (Worcester, Mass.). The meeting was promoted by the Heart and Endocrinology Sections of the National Institutes of Health, and there were 40 invited participants.

Hormones and Cholesterol Metabolism

Most of the discussion on hormones and cholesterol metabolism was concerned with the influence of the thyroid.

After Dr. KONRAD BLOCH had noted the various steps in the biosynthesis of cholesterol, Dr. G. POPJÁK (London) described certain inhibitors and suggested its physiological control occurred mainly early in the synthetic pathway. Professor SUNE BERGSTRÖM (Lund) said that the difference in excretion of bile acids in hypo- and hyperthyroid rats might be due to thyroid hormone stimulating intestinal bacterial activity. Dr. FORREST KENDALL (New York) pointed out that all tissues could degrade cholesterol into bile acids and that this was not an excessive property of the liver.

Dr. G. S. BOYD (Edinburgh) discussed the extra-thyroidal action of thiouracil in elevating the plasma cholesterol in rats and the selective stimulation of rat myocardium by certain thyroid analogues. Triac* reduced the plasma and aortic cholesterol in rats. According to Dr. LAWRENCE MILCH (Randolph Field), the aorta and coronary arteries of myxoedematous dogs contained a high concentration of certain low-density lipoproteins in contrast with normal dogs. Dr. R. GORDON GOULD (Los Alamos) said that in myxoedematous and xanthomatotic patients the rate of cholesterol turnover was greatly retarded. Dr. J. E. RALL (Bethesda) showed that thyroxine's protein-binding capacity depends upon its concentration in the plasma. This capacity could be altered by sex hormones, methyl testosterone reducing it and thereby increasing the concentration of free circulating thyroxine. Dr. ABRAHAM WHITE (New York) had observed that ^{14}C-labelled acetate was incorporated faster in the female rat than in the male or castrated female. In his experience hydrocortisone decreased the rate.

Atheromatous Plaques

Dr. R. L. HOLMAN (New Orleans) thought the filtration theory of the formation of fatty atheromatous lesions did not accord with the observation that arterial lesions might be scarce with the hypercholesterolaemia produced by alloxan or detergents. He stressed the importance of changes within the arterial wall leading to the focal deposition of cholesterol. He regarded atherosclerosis as a progressive histological process with definite sequential stages; it might be useless to expect the more advanced stages to be reversed by measures designed to lower hypercholesterolaemia.

Dr. N. T. WERTHESSEN (San Antonio) showed that the deposition of cholesterol in the isolated aorta is directly related to the initial concentration of the cholesterol passing through the vessel and to the intravascular pressure. The aorta was not just a passive structure, since the filtration of lipid into its wall was directly related to its glucose content. Dr. D. B. ZILVERSMIT (Memphis) suggested that the high concentration of phosphatide in the aorta might be due to local synthesis, and also stressed the vessel's capacity to synthesize phospholipids. He suggested that, once this lipogenetic process was set into motion, reduction of hypercholesterolaemia might well have little or no effect. Dr. LEON HELLMAN (New York) had cannulated the thoracic duct in humans and so been able to make a simultaneous analysis of the plasma and lymphatic lipids. His studies suggested that there might be a disorder at the intestinal level of absorption of cholesterol in hypercholesterolaemic hyperlipaemic subjects.

*Triiodothyroacetic acid.

Experimental Atherosclerosis

Dr. J. STAMLER (Chicago) said that in experimental birds hormones caused progression or regression of atherosclerosis only if the diet was atherogenic. Dr. DAVID ADLERSBERG (New York) said that in rabbits corticotrophin, cortisone, and prednisone elevate the free cholesterol without causing any very significant rise in ester cholesterol. Despite marked hypercholesterolaemia and hyperlipaemia these animals showed less atherosclerosis than those receiving cholesterol alone. By further showing that the simultaneous administration of hyaluronidase increased the extent of their arterial lesions, he was able to suggest that the reduction of atheromatous lesions with cortisone may be related to decreased permeability. Dr. S. O. BYERS (San Francisco) reported that rats subjected to the stress of constant movement had shortened clotting times. Dr. J. MARMORSTON (Los Angeles) said that a single injection of corticotrophin produced extensive and widespread vascular lesions (including cerebral haemorrhage) in dogs subsequently fed cholesterol and thiouracil. This did not occur if the corticotrophin was omitted.

Dr. R. PICK (Chicago) emphasized the difference between the aorta and the coronary arteries in the experimental production of atheroma. It was much easier to produce experimental lesions in the aorta, and Dr. R. L. HOLMAN (New Orleans) felt that this might be due to histological differences between the aorta and coronary arteries. Dr. R. H. FURMAN (Oklahoma City) cited the case of a young woman who had hypercholesterolaemic biliary cirrhosis in whom no atherosclerosis was subsequently discovered in the coronary arteries, although lesions were found in the aorta; this patient's cholesterol/phospholipid ratio was normal, despite the very gross hypercholesterolaemia. Dr. VICTOR DRILL (Chicago) had been unable to produce constant lowering of the plasma cholesterol by oestrogens without also producing some feminizing effects.

Hormones and the Blood Lipids

Dr. JOSEPH SEIFTER (Philadelphia) described an extract of hog posterior pituitary which caused lipaemia and was apparently unrelated to other pituitary hormones. This extract elevated the plasma fatty acids, cholesterol, and phospholipids primarily in the portal circulation but also in the systemic circulation in the presence of liver damage. Dr. R. H. ROSENMAN (San Francisco) had made studies on a group of accountants during times of mental stress such as the quarterly balancing of accounts. Although there was little information about any change in physical activity or diet, the plasma cholesterol was elevated and the clotting-times shortened in these subjects. Dr. DAVID ADLERSBERG (New York) discussed the association of hyperlipaemia with acute and chronic pancreatitis and concluded that more investigations were needed before this association could be explained satisfactorily.

Dr. E. STRISOWER (Berkeley) had administered large doses of desiccated thyroid, thyroxine, and triiodothyronine to euthyroid schizophrenic patients over periods of several months. He observed a decrease in the concentration of high-density lipoproteins in all patients. Dr. M. F. OLIVER (Edinburgh) had also observed a decrease in the concentration of alpha-lipoproteins with large doses of several thyroid

hormones, but with more physiological doses the alpha-lipoprotein concentration actually increased. Dr. HOWARD EDER (New York) reported that a small dose of methyl testosterone and a small dose of a weak oestrogen could cause changes in the alpha/beta-lipoprotein ratio without necessarily influencing the concentration of total circulating cholesterol. He suggested that this change in lipoprotein concentration may precede any alteration in plasma total cholesterol. Dr. R. H. FURMAN (Oklahoma City) showed that the administration of glucose prevents a hypercholesterolaemic response to methyl testosterone, and that in the absence of protein in the diet methyl testosterone actually causes a decrease in the plasma cholesterol concentration.

Clinical Studies

Dr. LOUIS KATZ (Chicago) felt that it was important in any conference concerning hormones and atherosclerosis to remember that emotions can influence hormonal balance. An attempt should be made to classify emotions and emotional types in relation to coronary disease. Sir HOWARD FLOREY, F.R.S. (Oxford), thought that more studies should be done to determine the influence of emotions and hormones on blood coagulation.

Dr. A. R. P. WALKER (Johannesburg) said that, although the Bantu lived long enough to reach the coronary age-group, coronary disease was rare; at necropsy only 19% showed aortic atherosclerosis and 6% coronary atherosclerosis. On the other hand, cerebral atherosclerosis and hypertension were common. There was no male predominance in the incidence of coronary disease in the Bantu. Compared with white people, the Bantu had a higher concentration of unesterified fatty acids, greater fibrinolytic activity, and a different oestrogen excretion pattern. Their diet was high in carbohydrates and low in animal protein and fats and they were more active physically. He considered the lack of atherosclerosis as due primarily to their unusual diet, although liver disease might play some part.

Dr. M. F. OLIVER (Edinburgh) reported that several thyroid analogues reduced hypercholesterolaemia without increasing gross oxygen requirements, but these substances increased the incidence of effort angina and could not maintain the cholesterol at a low level for any length of time. He had been unable to dissociate the cholesterol-depressing effect of weak oestrogens from their feminizing action. Over a two-and-a-half-year period, ethinyl oestradiol reduced the plasma lipid levels in a group of men with myocardial infarction, but there was no significant reduction in morbidity or mortality from coronary incidents when compared with a comparable control group. Dr. J. STAMLER (Chicago) had had much the same experience in patients who had received "premarin," a conjugated oestrogen preparation, over a period of three years. Thus there is no evidence so far that reduction of the plasma cholesterol influences the prognosis of coronary patients. Dr. ROGER ROBINSON (Worcester, Mass.) had also been unable to dissociate depression of the plasma cholesterol from feminization by the administration of "manvene," a weak oestrogen.

New Appliances

LIFTING-AID

Dr. W. RUSSELL GRANT (Winchester) writes: The following points were considered to be important in the construction of a lifting-aid. (1) The type of slings should be inexpensive to construct, easy to apply to the patient, and when applied should leave adequate clearance for toilet purposes, etc. (2) The actual apparatus should be able to be fixed to the bed and not be dependent on there being a strong ceiling, overhead beam, or strong wall. (3) The type of mechanical pulley should be one which is in mass production, and therefore inexpensive and readily available. (4) The overall cost should be such that it would be reasonably possible to obtain money under either Section 28 as an auxiliary nursing-aid or Section 29 under the powers delegated to the welfare officer.

After intensive investigation the simplest and most economical form of sling found consisted of two webbing straps; one to pass round the upper back, coming forward under the arms; the other to pass underneath the thighs just above the mid-point. By this means the patient's knees and hips assume a position halfway between the lying and the sitting position, which is found to be the most useful. The slings are constructed of old fire hose, which can be bought for sixpence a foot (30 cm.). These slings can be applied without having to lift the whole weight of the patient at any time.

Owing to the varying methods of construction and stability of beds, it was planned to make a frame which

could be very readily clamped on to the ordinary 1¼-in. (3-cm.) tubing used in the hospital type of bed. It has been found, however, that it can be equally well applied to the ordinary domestic type of wooden-headed bed. A 1¼-in. (3-cm.) electric conduit was used throughout in the form of a longitudinal goal-post, running parallel to the long axis of the bed, and from this goal-post a second half goal-post, running laterally at right angles and having its vertical component resting on the floor. The horizontal limb of the half goal-post carries some ordinary sliding-door track and a trolley, and provides the lateral movement of the hoist apparatus. A trolley is fitted with a ring on to which is attached the actual lifting mechanism. The vertical leg of the half goal-post is situated at such a distance from the side of the bed as to accommodate a wheel-chair.

The mechanical pulley is one in common production which is usually employed by firms to enable a normal person to lift a load of up to half a ton (508 kg.). This, of course, is far in excess of what is required, but it produces a power ratio to enable a person of 12 stone (76 kg.) to be lifted by a 5-lb. (2.3-kg.) pull. This is an ordinary geared block-and-chain tackle. Oil was not applied to the chain, as this was obviated by the chain being cadmium-plated.

The manufacturing process was reduced to putting five bends in 1¼-in. (3-cm.) conduit, which the ordinary hospital or electrical services should be able to do, and cutting off the pipes to the requisite length.

Various scaffolding clamps were employed in connecting the conduit, and it is important to remember that these clamps are normally used with types of water-piping, and

(*Continued on p.* 1061)

To-day's Drugs

Under this heading we hope to publish from time to time authoritative notes on a selection of new drugs.

Dexten Ionexten-Tabs (Clinical Products Ltd.).—Dexten is a proprietary preparation of dexamphetamine sulphate, and is here compounded in a resin-bonded form. This form of pharmaceutical preparation results in a slow release of the active principle over a period of 12 hours, and is similar in purpose to other long-acting preparations. Some side-effects are minimized in this way, as circulating concentrations may not reach undesirable levels. Each tablet contains 10 mg.

There is little evidence that dexamphetamine sulphate is any less stimulant than amphetamine, and both compounds may be of use in suppressing appetite in the treatment of obesity. Ancillary drugs, however, are seldom required when dietetic control is carefully supervised, and their stimulant effect may produce insomnia if they are taken in the latter part of the day. The chief indication for the preparation is in the management of mild depressive states and for narcolepsy.

Barbidex Ionexten-Tabs (Clinical Products Ltd.).—Barbidex tablets also contain 10 mg. of resin-bonded dexamphetamine sulphate, but include as well 65 mg. of phenobarbitone. There are available on the market other similar compound tablets containing both a barbiturate and amphetamine, and many physicians await the evidence that their conflicting pharmacological properties result in a happy therapeutic synergism.

Carmerin (H. R. Napp Ltd.).—This preparation contains 200 mg. of acetylcarbromal, which is a mild hypnotic, and also 150 mg. mephenesin with 0.05 mg. of reserpine. The compound therefore theoretically combines the effects of a sedative with those of a tranquillizer. Mephenesin, which depresses transmission of impulses at the spinal cord level, and therefore may produce skeletal muscle relaxation, is acting in conjunction with the reserpine, whose site of action is the hypothalamus, where sympathetic transmission is blocked and mental tension is consequently relaxed. Controlled trials of the effects of such drugs upon anxiety states have not produced consistent convincing evidence of their efficacy, and it is doubtful whether the addition of carbromal will have much further effect. The preparation is not cheap, and an extensive therapeutic trial would be required to assess its merits.

It is perhaps of interest that none of the components of this preparation are scheduled poisons, and the tablets could be bought quite legally without any requirement for a prescription.

(*Continued from p.* 1060)

their sizes are quoted according to the internal diameter of the water-pipe. In the case of the conduit, sizes are quoted according to the external diameter. Therefore, from the practical point of view, a 1-in. (2.5-cm.) key clamp will fit 1¼-in. (3-cm.) electric conduit.

The overall cost, including the time for construction, is £25. We obtained a second-hand hospital bed for £5, making the total overall cost £30. This apparatus has been in use for over three years, and a dozen of them have been used in the county of Hampshire without giving any trouble.

With regard to the parts required for making this hoist, the "Kee Klamps" were obtained from Messrs. Gascoignes, Ltd., of Reading; the attachment of the 3¼-in. (8.3-cm.) clamp to the bed is made by Messrs. S. B. Whitfield and Co., Ltd., of Lawson Tait House, 12–21, Conway Street, Fitzroy Square, London, W.1; and the actual hoist was supplied by Messrs. George King and Co., of Stevenage, and is known as the "King" bantam lift.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Standardization of Insulin

SIR,—I was glad to read in your issue of April 19 (p. 942) the letter by Dr. Arnold Bloom on the serious mistakes still commonly made in the dose of insulin by patients—otherwise seemingly intelligent—nurses, and even doctors. It is surprisingly common that patients answer wrongly when asked their dose in units at their first consultation. When I have checked the answer of "20" by looking at the syringe and finding that 80 per ml. strength is being used, the dose is 80 units and not 20. Indeed, mistakes were, and are, so frequent that I never feel sure of the dose of a new patient without checking the type and strength of insulin and seeing the syringe and its markings, and sometimes a minim syringe is used. The misleading word "units" often appears on the barrel of the syringe, which, with the strength of insulin being used, the dose seldom is. To obviate mistakes excellent standard 1- and 2-ml. syringes (B.S.1619) are available, with no mention of units, but with 20 clear cross-divisions per 1 ml. so that each division equals 1, 2, or 4 units, depending on whether 20, 40, or 80 per ml. strength is being used. No other syringe should be used for insulin injections. In this way errors will be minimized, but I also think that insulin should be prescribed not only *as units* but also as *so many marks on the patient's syringe*.—I am, etc.,

London, W.1. R. D. LAWRENCE.

Foetal Distress in Domiciliary Midwifery

SIR,—I read with interest Drs. T. B. L. Bryan and W. G. Dawson's report of a case where oxygen was used for foetal distress in domiciliary practice (*Journal*, March 29, p. 758), and particularly noted their conclusions that success was partly due to the psychology of the patient's wishes being considered to a large extent.

My own feeling, especially in view of the statistics given,[1] was that there was a good slice of luck that the baby who survived fell into the 50% or thereabouts who do, despite the oxygen and psychology. Surely, in view of the facts, this patient might have been better advised to have her baby in hospital. First, she was well into middle age, a gravida-5 with a bad obstetric history. Then she was allowed to be in labour for a total of 31 hours, having shown marked foetal distress for 5 hours and 45 minutes prior to delivery, and apparently 2 hours and 45 minutes elapsed before being seen by the doctor for this foetal distress.

If at this stage she had been transferred to hospital and found not to be fully dilated, I think in view of the foetal distress a caesarean section may have been performed, and surely at this early stage of distress at least a 90% chance of survival anticipated. Admittedly a caesarean section was avoided but at a greatly increased risk to the foetus. The baby was delivered after this long, exhausting labour face to pubes and without the pressure-saving episiotomy, and this could hardly enhance its chances. Had the baby not survived could anyone really have been very surprised?

I am a G.P. practising obstetrics and book over 80 cases a year, the great majority being delivered at home or in one local G.P. maternity home, but surely we must select cases and must guide the poor-risk patient to hospital despite the psychological wish for a home confinement. If we do take a calculated risk, in view of strong non-medical reasons, we must surely be guided by multiple warnings as evident in this case. Long labour with uterine inertia, premature rupture of membranes, thick meconium, foetal heart

irregularities—surely these are grave prognostic signs which should send us hurrying for the ambulance, where the portable oxygen and psychology *en route* would be of great help.—I am, etc.,

Brentwood, Essex. JACK FINE.

REFERENCE

[1] FitzGerald, T. B., and MacFarlane, C. N., *Brit. med. J.*, 1955, 2, 358.

SIR,—The use of oxygen in general practice for the treatment of foetal distress does not provide as simple a solution as Drs. T. B. L. Bryan and W. G. Dawson would suggest (*Journal*, March 29, p. 758). The efficacy of administering oxygen to the mother in cases of foetal distress is by no means universally accepted, but I do not wish to discuss this here. The case reported may lull general practitioners into a sense of false security. The expectant treatment of foetal distress at home is fraught with dangers. Once signs of foetal anoxia have been detected constant vigilance must be maintained and immediate action taken as soon as a deterioration becomes apparent. In the first stage of labour such action can only be undertaken in hospital where there are not only facilities for caesarean section but a fully equipped team to deal with asphyxia neonatorum, should this occur. As a general-practitioner obstetrician it has been my rule to transfer to hospital cases of foetal distress where a vaginal delivery is not likely to be effected within the time required for such a transfer. The mortality figures quoted in the paper are sufficient to justify this course of action.

The use of an open ether anaesthetic, if this is what is meant by "ether alone," is open to criticism. It has been my practice in general practice to use only local analgesia—1% lignocaine hydrochloride without adrenaline—for all operative procedures. Even for manual removal of the placenta this method, together with gas and air, is usually adequate. In the case described, assuming that the instruments were prepared as soon as the foetal distress was discovered, it would have been logical to apply forceps, using a pudendal nerve-block. This would have taken no longer than inducing a general anaesthetic, and oxygen could have been administered to the mother right up to the birth of the infant. An anterior lip of cervix would have been no contraindication to this technique.

The left lateral position may well be safer when a general anaesthetic is used, but I find the lithotomy position (using a portable lithotomy frame) far more satisfactory. Credé's manœuvre, manual removal, and the repair of a torn perineum are more efficiently performed in the latter position; it is also more comfortable for the operator. Had my patient been under a general anaesthetic I doubt if I would have left the placenta *in situ* for 20 minutes, nor would have I performed a Credé's manœuvre. The authors state: ". . . a Minnitt apparatus could probably be used with benefit to enrich the atmospheric oxygen." This machine is for gas and air and will not take an oxygen cylinder. Its use, in fact, would have the opposite effect to that suggested.

I appreciate that the case reported occurred in a rural practice (Wareham, Devon) and this should have been mentioned. In these days, if a patient can be speedily transferred to hospital, there is no place for the treatment of foetal distress at home.—I am, etc.,

Liverpool, 18. MERVYN GOODMAN.

Dirty Habits

SIR,—Dr. J. Crawford's letter appearing under the above caption in your issue of April 19 (p. 943) has no doubt engendered vibrations of sympathetic horror in the minds of many of your readers. Not having had the opportunities enjoyed by Dr. Crawford for observing the post-emunctory habits of my fellow citizens, my experience has come from another direction. Recently I entered a delicatessen shop for the purpose of buying sliced ham and was obliged to wait for some minutes while the customer before me was served with the same commodity. The lady behind the counter, after thoroughly licking her fingers the more adroitly to place a sheet of greaseproof paper on the scales, deposited a quantity of ham thereon. Finding it to be in short measure she picked up another slice (with the same fingers), and, after squeezing it affectionately with both hands, laid it reverently on the top of the pile. The customer accepted her package without comment. My courage, however, failed me, and I hastily changed my order to sliced bacon, which one can at least feel has been effectively sterilized by grilling before being eaten. I have since transferred my patronage to an enlightened firm which insists on all exposed food being handled with plastic tongs, to the great comfort and peace of mind of its bacteriologically informed clients. This, however, is hardly fair to the management of the erring firm, who cannot be expected to appreciate the reason for my apparently heartless defection.

We are told that active propaganda against smoking has effectively produced cancerophobia among smokers and consternation among tobacconists. Would not an equally sustained propaganda against habits known to be the direct cause of infection be of more immediate benefit to the public health? And might not the biography of a typhoid bacillus, dramatically relayed by the B.B.C., sting the national conscience more effectively than the televising of a complicated operation the intricate steps of which many of us might have to confess ourselves at a loss to follow with any degree of accuracy?—I am, etc.,

London, N.W.11. SYLVIA D. CHAPMAN.

SIR,—I must support Dr. Jno. Crawford in his letter in the *Journal* of April 19 (p. 943). The public in general just does not appreciate the dangers of not washing the hands after going to the lavatory. There should certainly be a Government publicity campaign, but also it should be taught, retaught, and taught again in schools.

I come from a middle-class family and my parents never washed after going to the lavatory, though they did before meals and made us do so too. I went to the local grammar school until I was 15, where we did two years of "hygiene," but the subject was never mentioned there. Afterwards I spent three years at a large public school, and I cannot remember anyone washing their hands there; certainly I never did, nor did my friends. It was not until my third year at the university when we started bacteriology that I even knew that people did it.

I must be fairly representative of a member of a non-medical family with a reasonable education, so how can we expect the ordinary man and woman to know anything about it without blazening it forth from the roof-tops? I feel very strongly about this, as my husband is a member of a firm of small multiple butchers, and he tells me that the sanitary authorities are now requiring a wash-basin and hot water to be installed alongside a sink used for washing utensils—the wash-basin to be used only for washing hands and the sink only for knives, etc. Knowing human nature as I do, it is obvious that sink and wash-basin will be used indiscriminately for both purposes, and the object of the sanitary people will be defeated before it has started because they have never bothered to explain to the workmen why the wash-basin has been installed. Legislation without education!—I am, etc.,

Reading, Berks. MARGARET P. COSHAM.

SIR,—May I call your attention to a most insanitary development along our highway, the lay-by? There always has been wayside micturition and defaecation, but the lay-by, particularly if there is a copse or other visual cover near, concentrates this into a smaller area, and the conditions near some of the lay-bys on the Great North Road are filthy.—I am, etc.,

King's Langley. REGINALD FISHER.

Antibiotics in Animal Husbandry

SIR,—With regard to your annotation (*Journal*, April 5, p. 822) that medical opinion should be consulted before the newer antibiotics are used in treating bovine mastitis, I would draw your attention to the fact that streptomycin, oxytetracycline, and chlortetracycline are already being

employed as intramammary injections for the treatment of this disease in Britain, but to a lesser extent than penicillin. In America, chloramphenicol, neomycin, polymyxin, and erythromycin are also advertised for this purpose. There is little or no information available as to whether or not the use of these newer antibiotics is leading to an increased incidence of drug-resistant strains of *Staphylococcus aureus* in cow's milk.

Your reference to Gould's observation[1] that the nasal staphylococci in workers in a penicillin factory were penicillin-resistant raises an interesting question regarding present methods of animal feeding. A considerable proportion of pigs and table poultry in Britain are fed continuously on diets containing either tetracyclines or penicillin. Do the workers responsible for compounding and/or handling these foods in the mills and on the farms also possess a bacterial flora that is antibiotic-resistant?—I am, etc.,

Stock, Essex. H. WILLIAMS SMITH.

REFERENCE

[1] Gould, J. C., *Nature (Lond.)*, 1957, **180**, 282.

Serial Cholecystography

SIR,—Great credit is due to your contributor, Mr. J. Dudfield Rose (*Journal*, February 15, p. 360), for exposing the all-too-frequent uselessness of the orthodox method of cholecystography, and for showing that only by serial cholecystography can a reliable report be obtained about the functioning of the gall-bladder and of the bile ducts. However, your correspondent, Dr. C. Bellamy (*Journal*, March 29, p. 769), is justified in objecting to the use of 19 *x*-ray exposures on account of the excessive radiation which the patient would receive. This objection can be met by reducing the number of exposures to 6, by using a 1½-mm. aluminium filter in the tube, by reducing the tube-to-film distance, by using a small localizing cone, by using kilovoltage of 80 or 90, and by not using a high-ratio grid. In this way the surface dose received by the patient is less than that involved in a proper barium meal examination, and is well within the recommended safety limits. The gonads will never receive any radiation as long as a small localizing cone is used.

The six exposures which I have found very helpful in obtaining a reliable gall-bladder report are: (1) a control; (2) twelve-hour prone after ingestion of the opaque medium; (3) twelve-hour erect; (4a) 15 minutes (4b) 25 minutes, (4c) 45 minutes after a standard fatty meal (1½ oz. (44 ml.) "prosparol," plus 2½ oz. (71 ml.) "Jaffa Juice," plus 4 oz. (114 ml.) hot water is satisfactory). The first two exposures are on a 12×10 in. (30.4×25.4 cm.) film, the other four are on a 10×8 in. (25.4×20.3 cm.) or even on an 8½×6½ in. (20.4×15.3 cm.), because by that time the gall-bladder will usually have been located. The whole procedure on the second day need not take more than 60 minutes. A healthy gall-bladder will contract to about 65% in the first 15 minutes, to about 40% in the first 25 minutes, and to about 30% or less in the first 45 minutes after a standard fatty meal. It is the contraction within the first 25 minutes that gives valuable information about the presence or absence of vesicular stasis. Hence the futility of taking the first after-fatty-meal film after the lapse of two hours, because this cannot tell us what has been happening in the first 25 minutes.

Your correspondent, Dr. A. A. Vickers (*Journal*, April 12, p. 888), is wise in objecting to excessive radiation, but I must cross swords with him for implying that serial cholecystography may give only "a little information . . . about some minor point in diagnosis." Chronic semi-invalidism is not a minor point to the chronic cholecystic patient, and a truly reliable report about the gall-bladder and its ducts is not "a little information." On the contrary, it is very necessary to the understanding medical man who has charge of the case. To sum up, the above serial method of cholecystography is perfectly safe for the patient, it takes less than half of the patient's time that of the orthodox method takes, and it gives reliable information in at least 95% of the cases.—I am, etc.,

London, W.1. ISAAC EBAN.

"Diminished Responsibility" Manslaughter

SIR,—Dr. W. A. O'Connor's letter (*Journal*, March 29, p. 770) is a classic of muddled thinking. His main concern would appear to be that no "stigma" attaches to the act of murder if diminished responsibility exists, rather than that the person concerned should have the appropriate psychiatric treatment. One wonders if Dr. O'Connor regards patients suffering from malignancy or tuberculosis as being similarly "stigmatized," as, unfortunately, many of the public do, or as people requiring medical treatment. I would suggest it to be more logical for a psychiatrist to assess whether a "diminished responsibility" case is fit for discharge rather than a judge, who is an expert on law and not on mental illness.—I am, etc.,

Ayr. ALASTAIR C. S. TAYLOR.

SIR,—As it is about the anniversary of the Homicide Act, may I endorse and amplify the remarks made in regard to the case of Bastian by Dr. Patrick McGrath (*Journal*, March 15, p. 641)? He appositely points out the very great difference between a life sentence in gaol for a prisoner showing abnormality of mind, and his going to a hospital (obviously referring to Broadmoor) where he could receive expert psychiatric treatment. As I was a witness in Bastian's case, and I shall not be revealing anything which did not come out in court, I think Dr. McGrath's points might usefully be amplified by giving some details of the case.

Normally a good father, and not prone to violence, but very upset by aspects of his wife's behaviour, Bastian one afternoon suddenly killed his two children with a rolling-pin, the state of the room suggesting that he had been in a frenzied state. Only a month before, Bastian had been in hospital with features suggesting an endogenous depression, although, in fact, right up to the trial the exact diagnosis, whether depression, schizophrenia, or hysteria superimposed on one of the others, remained unsettled.

The trial, had the matter not been so serious, would almost have verged on the Gilbertian. Bastian wanted to plead guilty to murder, and was only with difficulty dissuaded from doing so. Dr. Trevor Gibbons and I both thought, from our initial examination, that he had at least suffered from sufficient abnormality of mind "substantially to impair his responsibility." However, after discussing the matter with Dr. Brisby, the Principal Medical Officer at Brixton Gaol, who had him under close observation and has wide psychiatric experience, we concurred that in fact Bastian's abnormality might well amount to disease of the mind, and that he had not known the act was wrong at the material time. Counsel agreed that this plea would be in Bastian's interests, but Bastian refused to allow him to plead insanity. His counsel therefore could only plead abnormality of mind, although he made it clear to the jury that he was only acting on instructions and not expressing his personal opinion. On the strength of this defence, the judge ruled that the prosecution could cross-examine to establish insanity, and both Dr. Gibbons and I conceded that Bastian, in fact, could be regarded as legally insane at the time he committed the act, and Dr. Brisby stated this in even more emphatic terms. The jury thereupon retired for some 20 minutes and brought in a verdict of manslaughter. The judge, clearly feeling that with such an unstable individual an indeterminate sentence was the only possible one for the public and his own sake, sentenced Bastian to life imprisonment, and the circle was complete, Bastian receiving precisely the same sentence he would have received had his plea of guilty to murder been accepted.

The late Sir Norwood East used to complain that doctors would mix up responsibility and culpability (i.e., the degree of wickedness). The lawmakers now seem to have done so too, for it is, of course, really diminished culpability that the Act is catering for and not diminished responsibility, for which treatment would be the logical corollary. In fact, one feels that this clause was designed as a let-out in capital murder—and in general to allow the sentence to be graded. Nevertheless, it only lessens the punishment. Dr. Reginald Bennett, M.P., raised this anomaly in the House when this Bill was before the Commons. The answer he received—which I submit was quite unsatisfactory—was that once a charge was reduced to manslaughter the judge had full discretion as to disposal. Thus he could, if he thought fit, bind a prisoner over to have treatment in a

mental hospital. Theoretically this might sound all right, but in real life what judge would feel justified in binding an epileptic, or a prisoner with a post-concussive personality-change who was not insane, or for that matter Bastian, to go as a voluntary patient for a maximum period of a year to a mental hospital, which has no legal right to detain a voluntary patient? And what hospital would accept him?

It might be argued that in a case such as Bastian's the convicted person could be certified and committed to Broadmoor after sentence, but the difficulty with these borderline cases is that it is extremely difficult to certify them, and the prison authorities, I imagine, are particularly hesitant lest they be charged with putting away someone already detained in another way. The outcome of all this, therefore, is that prisoners such as Bastian are, in fact, worse off than they would have been before the Homicide Act. I am quite sure that before the new Act the jury would have accepted the opinion expressed by three doctors, that he did in fact come under the McNaughton Rules. I believe the Act has come under criticism in other ways. I would suggest that the anniversary is the time to draw attention to this patent defect, and Dr. McGrath is to be congratulated on rendering a valuable service in drawing attention to this matter.—I am, etc.,

W. LINDESAY NEUSTATTER.

London, W.1.

Problems of Puberty

SIR,—I was greatly interested in the above correspondence (*Journal*, February 15, p. 397, and March 22, p. 710), and in the conflict of views expressed, which, in my opinion, is more apparent than real. In my experience, the vast majority of boys masturbate on reaching puberty, but only a minority continue it for any great length of time. It is, of course, very wrong to suggest to a boy that he has incurred any harm as a result of masturbation; nevertheless, if normal sexual maturation is to proceed, some information and help must be given.

Masturbation reflects the early, auto-erotic stage of sexual maturation, and, if development is to proceed normally, it is essential that this stage should be got over as quickly as possible. This, of course, cannot happen as long as the boy masturbates, nor can it happen if sexual fantasies are indulged in or sexual desires deliberately stimulated by pictures, books, sex stories, films, etc., with or without masturbation. It is therefore wise, I think, gently but firmly to dissuade the boy from masturbation, and at the same time to give him some conception as to how normal sexual development should proceed. In particular, he should be warned against giving way to sexual fantasies (day dreams) of any kind (even if only aroused by attractive real-life views of the opposite sex), which are in most cases the prime origin of masturbation, but which may persist without masturbation into adult life, often with disastrous results. A full appreciation of what normal sexual maturation means may not be possible at this stage, but I think it is worth emphasizing that he should leave his sex life completely alone, that if left undisturbed it will take care of itself, and that, in later life, sex desires should never be aroused except on the basis of a deep affection (and mutual consideration of welfare) such as will normally occur in marriage. The failure to link the sex life with the tender emotions which give it strength, consistency, and stability (or their subsequent separation) is of course the common tragedy of sexual development. If this failure is present in either partner, marital difficulties are almost inevitable, with consequent disappointment and frustration. The problem can, as a rule, be solved by patience, consideration, and mental discipline. It is rarely solved by seeking another partner.

During the war I was called by the defence in the case of a young American soldier, aged 21, who was found guilty of strangling a little girl of 7. He was an intelligent, likable, completely rational, and attractive young man who had indulged in promiscuous adventures of every sort (conduct which he never regarded as in any way abnormal) from the age of 14. Very unfortunately, following a period of confinement to barracks (which was immediately followed by a bout of alcoholism), he found himself in a field with this little girl. When he tried to interfere with her sexually, the little girl began to cry, and in a fit of panic (aided no doubt by sexual and alcoholic excitement and confusion) he caught her by the throat and strangled her. Prior to this incident, he had always liked children, and had never regarded any child in a sexual way. He had consorted with camp-followers, prostitutes, and "good-time" girls, as and when opportunity offered. He was subsequently executed.

Here, I think, we have a terrible example of what lack of sexual maturity can lead to. I do not think this boy differed in any essential from 70% of his comrades, nor do I think the so-called sex maniac—apart from the rare case of the high-grade feeble-minded or the arrested or concealed schizophrenic—displays any other psychopathology than simple failure to mature (on which of course is based the legion of fantasies and impulses, and often of course weird theories and philosophies), a failure that should at almost any stage respond gratifyingly to correct psychological treatment, always, of course, provided that the patient understands the need of such treatment and wishes to have it.—I am, etc.,

ROBERT THOMPSON.

Pinner, Middx.

Antenatal Blood-grouping

SIR,—For many years now most laboratories have been undertaking antenatal blood-grouping. The primary object of this has been to meet the emergency of post-partum haemorrhage when, on the rare occasion, there is not time for cross-matching of the blood.

I have been considering for some time whether the ABO part of the grouping is necessary and in point of fact leads to a safe procedure. A very small percentage of this grouping information is ever used, and, as there is also the ever-present danger of clerical and specimen-labelling error, it would appear to be a much safer procedure to use, in the first place, O Rh-negative blood when a transfusion is given uncrossmatched. Thanks to the transfusion services O Rh-negative blood is available for Flying Squad maternity cases. The rhesus grouping would, of course, still have to be done in view of potential antibody-production in rhesus-negative patients. Short of tattooing the group on the patient, there is no infallible system of blood-group recording.

I am submitting this letter to stimulate comment in your columns from colleagues who are dealing with this problem. —I am, etc.,

B. A. THOMPSON.

Watford.

Maternal Anaesthetic Deaths

SIR,—I agree with Dr. D. D. Davies (*Journal*, April 5, p. 830) that vomiting is a danger during induction in maternity cases when a short-acting relaxant is used to facilitate intubation. I lost a patient who vomited copiously at the dangerous moment when suxamethonium had paralysed the larynx but not the abdominal wall. He was an in-patient in whom there was no reason to expect vomiting; but he had evidently had a drink before leaving the ward.

Some think this danger would be avoided in maternity patients if they were anaesthetized sitting up. In my patient, however, vomiting was projectile, and had he been sitting up the vomitus would still have reached the pharynx and flooded the lungs. I believe a safer way is to have maternity patients lying on their left side and tilted head-downwards for induction. This does not greatly increase the difficulty of intubation, and once the tube is in and the cuff blown up they can safely be placed in any position. For some years I have used this position in conjunction with the cyclopropane–suxamethonium–cuffed tube–nitrous oxide method that I previously described (*Journal*, April 28, 1956, p. 984). I have found it helpful not only in maternity cases but also in others in which vomiting was likely, such as acute obstruction, or emergency cases unprepared for anaesthesia.—I am, etc.,

J. G. BOURNE.

London, S.E.1.

SIR,—I was interested to read Dr. O. P. Dinnick's letter (*Journal*, April 5, p. 830), in which he quotes the *Report on Confidential Enquiries into Maternal Deaths in England and Wales*,[1] as stating that the number of maternal deaths due to inhalation of vomit during anaesthesia averages 11 per annum. This figure is, as he points out, appreciably lower than the estimate which I gave in 1956.[2] I hope that the figure which I gave may soon be found too high, but there is unhappily, so far as I can see, no such evidence as yet. The figure I suggested was 4% of maternal deaths—i.e., approximately 20 deaths per annum out of a yearly figure of 500 maternal deaths in England and Wales at that time. (Associated deaths were excluded from my figures.)

The authors of the report, in describing 32 deaths from inhalation asphyxia out of 49 anaesthetic deaths, point out that there were at least 20 deaths in which anaesthesia was probably a contributory factor excluded because of scanty information. Further, though the report deals with 1,410 deaths due to or associated with childbirth, the Registrar-General's records show that there were at least another 523 such deaths which were not referred to the inquiry. An appendix to the report gives evidence which shows that the missing cases are not likely to be weighted by any particular group of cases. This suggests that the number of anaesthetic deaths may be 65 to 70 for the 3-year period and the number due to inhalation 15 per annum before allowing for those in which anaesthesia "probably" played a part. The actual figure is of course unimportant in itself, but every preventable maternal death is of importance, and I am glad, therefore, that Dr. Dinnick has drawn attention to this section of the report.

May I make one further comment in relation to the anaesthetic agents which Dr. Dinnick has considered? When assessing the safety of different drugs and different methods of anaesthesia, is it not unreal to divorce this from the status and skill of the administrator? Pentothal and relaxants appear to be less safe than their rivals, but I find it difficult to believe that this is really so for the skilled administrator working with the equipment and in the conditions of his choice.—I am, etc.,

Birmingham. R. B. PARKER.

REFERENCES

[1] *Report on Confidential Enquiries into Maternal Deaths in England and Wales, 1952-1954.* Ministry of Health Reports on Public Health and Medical Subjects. No. 97, 1957. H.M.S.O., London.
[2] Parker, R. B., *Brit. med. J.*, 1956, **2**, 16.

SIR,—Dr. O. P. Dinnick (*Journal*, April 5, p. 830) mentions figures from the *Report on Confidential Enquiries into Maternal Deaths*[1] which, he says, "appear to show that thiopentone and the relaxants are relatively more dangerous than inhalational anaesthesia in obstetric practice." May I suggest that anaesthetic agents should not be condemned without full knowledge of the technique used, the skill of the anaesthetist, and the circumstances prevailing at the time?

The danger of aspiration of stomach contents is widely recognized. There is therefore no excuse for not taking precautions to prevent it. In this unit during 1955, 1956, and 1957 there have been approximately 320 anaesthetics for caesarean section. During that time there has been no maternal mortality or morbidity from aspiration of stomach contents. The procedure adopted for all patients is as follows:

(*a*) A fluid diet is given from the onset of labour.
(*b*) A narrow oesophageal tube is passed into the stomach, which is emptied before induction of anaesthesia—this applies to all emergencies whether for caesarean section, forceps, breeches, etc.
(*c*) The sucker is switched on and the laryngeal handpiece is placed under the patient's pillow.
(*d*) For thiopentone/relaxant induction, a 15° anti-Trendelenburg tilt is adopted. This reduces the risk of regurgitation before intubation.
(*e*) Only new and tested cuffed endotracheal tubes are used.

I believe that a thiopentone/relaxant technique followed by gas–oxygen maintenance in skilled hands and following the above routine gives a shorter, safer anaesthetic for mother and child while offering the obstetrician the best possible operating conditions.—I am, etc.,

Paddington General Hospital, London, W.9. JOHN ZORAB.

REFERENCE

[1] *Report on Confidential Enquiries into Maternal Deaths in England and Wales, 1952–1954.* Ministry of Health Reports on Public Health and Medical Subjects, No. 97, 1957. H.M.S.O., London.

Acute Otitis Media

SIR,—Referring to the very appropriate comments of Dr. J. McA. Williams (*Journal*, March 29, p. 773), may I state what I regard to be the anatomically and functionally correct explanation for the high incidence of acute otitis media in childhood (*Journal*, February 8, p. 328)?

The child's Eustachian tube is short and patent. The adult's Eustachian tube is long and, as a rule, closed; it only opens during certain muscular actions (particularly yawning and swallowing). Transition from the one to the other starts at the age of 8 or 9 years. Childhood's short and patent tube readily exposes the middle ear to direct invasion by pathogenic micro-organisms from the throat.—I am, etc.,

London, S.W.12. A. B. ALEXANDER.

Porphyria

SIR,—In reply to Professor C. Rimington's letter (*Journal*, March 15, p. 640) regarding the classification of the porphyrias: he suggests that hereditary hepatic porphyria should be classified into two groups—(1) porphyria cutanea tarda hereditaria; (2) acute intermittent porphyria.

He would class the White South African type of porphyria as "porphyria cutanea tarda hereditaria." The serious disadvantage of this method of classification is that in most of our female cases of acute porphyria there are no cutaneous lesions. This is why I proposed that the porphyrias should be classified on a genetic basis. There is the genetic type that is responsible for the family syndrome that is common in Sweden and the genetic type that is common in South Africa. In other countries both types occur. In both these types acute porphyria may be precipitated by drugs, and during the acute attack there is a great excess of porphobilinogen in the urine.—I am, etc.,

Port Elizabeth, South Africa. GEOFFREY DEAN.

Carcinoma of the Breast

SIR,—The letter on carcinoma of the breast by Drs. W. H. Bond, P. B. Kunkler, and J. A. H. Waterhouse (*Journal*, March 15, p. 643) raises many unsolved points of vital importance. They state that "it would indeed be surprising if an induced menopause did not improve the prognosis. There is unpublished evidence in at least one centre in the country indicating a real improvement in the survival rate at five years when an irradiation menopause is induced as part of the initial treatment." This statement must be interpreted with caution, reserve, and doubt. In this country I am aware of only one controlled series of breast cancer patients who were subjected to "prophylactic menopause"; to the best of my knowledge the increase in the 5-year survival rate in this series is only just statistically significant. Smith and Smith,[1] investigating the relationship between prophylactic surgical castration and the length of survival, observed a statistically significant improvement only in those patients with histologically positive axillary lymph nodes.

In patients with multiple metastases it is generally agreed that not more than 40% show any response to oophorectomy, and the average period of growth restraint obtained is nine months. It would therefore be most surprising if routine ovarian ablation could contribute any appreciable improvement in the long-term results, even if castration was performed at an early stage before metastases were clinically apparent.

Five, ten, and fifteen year survival rates must not be allowed to blind us to the essential fact that we are dealing with human beings. To a relatively young woman the removal of her breast is a major physical and psychological tragedy (the greater if executed radically); she is then made to undergo a 3 to 6 weeks' course of *x*-ray therapy with its attendant discomforts. After such mutilation and punishment (the true benefit derived therefrom is still not yet known), it is manifestly wrong in the light of present knowledge to add further physical and psychological trauma by inflicting prophylactic castration. Such a procedure can only be justified if it gives a striking improvement in survival rates, and this has certainly not been established. The optimum time to perform castration is when metastases are clinically present and active, but not before then. Furthermore, when performed at this time castration will show if a tumour is or is not oestrogen-dependent, a most important factor.

The role of prophylactic ovarian ablation in breast cancer justifies investigation, but, until fully evaluated, this procedure should only be undertaken in large centres under strictly controlled conditions. At the present time the occasional haphazard application of this measure must be strongly condemned.—I am, etc.,

Guildford. NORMAN MACKAY.

REFERENCE

[1] Smith, G. V., and Smith, O. W., *Surg. Gynec. Obstet.*, 1953, **97**, 508.

Carcinoma of the Breast

SIR,—Mr. W. H. Bond and his colleagues (*Journal*, March 15, p. 643) conclude from their interesting figures "that there is an urgent need for an investigation on the broadest possible basis to determine the optimum management of breast carcinoma." We have to consider the possibility that the answer to our prayer for better results in cancer treatment lies in the development of conservative rather than radical methods.[1,2]

Experimental cancer research is still guided by the same doctrines as were introduced by Paul Ehrlich more than 50 years ago. But a malignant tumour is not an infectious disease; therefore it cannot be understood or controlled on analogous lines. A malignant tumour is the outcome of a physiological process of regeneration[3,4] which has become deranged at an early stage, so that the regenerating cells derived from the basal cells of the germ layer have remained, more or less, undifferentiated or maldifferentiated. Such tumours are not quite "autonomous"; the organism has not entirely lost control over them. Evidence of this fact can be seen in the natural progress of untreated breast carcinoma and other tumours, which is much slower than could be expected from a continuous multiplication of "virulent" cells.

The most convincing proof yet of the reserve of growth control in the body comes from therapeutic experiments. The experiment of bilateral adrenalectomy in breast cancer is particularly interesting and may well mark the turning-point in our therapeutic approach to cancer. The metabolic changes following adrenalectomy reveal the presence of unbelievable powers in the organism, causing immediate cessation of pain and dramatic regression of advanced lesions. By exploring the nature of these changes and reproducing them by other means than removal of two vital organs, we may very soon find a new weapon in the fight against cancer. Meanwhile the radiotherapist can give us valuable information, not by experiments with more and more powerful machinery, but by experiments designed to determine the minimal dose of radiation which represses the growth of tumours.

The rationale of long spacing in radiotherapy is that the inflammatory reaction with round-cell infiltration, which follows every cell destruction by radiation, must be allowed to subside, so that fibrosis can seal off the lesion before the next dose of radiation is given.[5,6] If it could be established that only one-quarter of the conventional "lethal" dose is necessary to bring palliative relief in breast carcinoma, we could safely repeat the procedure four times in case of recurrences. But the optimal palliative dose lies perhaps even lower, and the end results of merely palliative treatment may be surprising.—I am, etc.,

London, N.W.1. F. M. LEHMANN.

REFERENCES

[1] Lehmann, F. M., *Postgrad. med. J.*, 1955, **31**, 11.
[2] Kennedy, B. J., Kelley, R. M., White, G., and Nathanson, I. T., *Cancer (Philad.)*, 1957, **10**, 1055.
[3] Nicholson, G. W., *Studies on Tumour Formation*, 1950. London.
[4] Büchner, Franz, *Allgemeine Pathologie*, 1950. München.
[5] Rubens-Duval, H., *Ann. Méd.*, 1914, **1**, 75.
[6] Jolles, B., and Koller, P. C., *Brit. J. Cancer*, 1950, **4**, 77.

Doctors and Human Survival

SIR,—Dr. Brian Heber's letter (*Journal*, April 5, p. 833) puts forward the pacifist view, often also called the "Christian" or "humanitarian" view. The problem of nuclear weapons, primarily a political question, has grave medical aspects which must of course cause us the greatest concern. It is hardly surprising that great efforts are being made in some quarters to enlist the support of doctors, via their strong humanitarian instincts, for a pacifist campaign. I hope, therefore, you will allow me to contest two of Dr. Heber's statements.

Doctors, Christian or otherwise, with their strong love of freedom, are hardly likely to agree that "it matters little which policy entails the least risk"—not when the risk is of Communist world domination with its denial of human freedom and of Christianity itself. Secondly, our politicians are, I think, less occupied in thinking about bigger bombs than in their efforts to achieve a just peace—grievously hampered though they be by a certain section of foggy-minded idealists very active at the moment.

As doctors, we should be constantly concerned with the medical problems of radioactivity. As citizens, surely a good motto would be, "If you can't help, don't hinder."—I am, etc.,

London, E.2. DOROTHY E. PEAKE.

Anoxia in Pulmonary Emphysema

SIR,—We would like to report similar experience to that of Dr. Dermot M. Collins (*Journal*, March 22, p. 709) on the use of intravenous injections of nikethamide (*B.P.*) in cases of pulmonary emphysema with associated states of disordered consciousness.

We have recently treated ten patients suffering from acute exacerbations of bronchitis and emphysema. When first seen they were either mentally confused, semi-conscious, or comatose. Several of them were treated initially with intravenous aminophylline (0.25 to 0.5 g.). This produced a temporary increase in rate and depth of respiration, but no detectable change in consciousness. All, however, regained consciousness within a few minutes of the rapid intravenous injection of from 6–14 ml. of nikethamide (*B.P.*). The injection had to be repeated after a period of up to six hours in some cases, and a careful watch was kept during this time on the state of consciousness and chest movement.

Three patients were maintained on intramuscular nikethamide (*B.P.*) (2 ml. hourly), but the majority did not require further treatment for at least 24 hours after the initial injection, and in four cases only one intravenous injection was required.

We would like to thank Dr. J. Bevan Jones for permission to report this.

—We are, etc., L. SINCLAIR.
Croydon, Surrey. H. JACOBY.

Chain-store Glasses

SIR,—I would like to support Mr. John Primrose's letter on this subject (*Journal*, April 19, p. 943). It is not possible for wrong glasses to do any harm other than in children up to the age of 6 or so, when one wrong lens can cause blurring of vision which may lead to inhibition of the sight of that eye—an inhibition which may ultimately lead to irreversible amblyopia.

Yesterday, at hospital, I saw a patient whose vision was reduced to counting fingers in the right eye and who had no perception of light in the left. This was due to advanced simple chronic glaucoma. He had never been seen by an ophthalmologist.—I am, etc.,

Southport. DAVID RANKINE.

Epistaxis

SIR,—Should the method of treating epistaxis which Dr. Humphrey Osmond ascribes to Mr. T. B. Layton (*Journal*, April 12, p. 891) properly be regarded as the late Wilfred Trotter's? His description is as follows[1]: "Prop the patient well up with a comfortable inclination to one side, arrange a large pad of wool for him to dribble into, put a dental prop between the teeth, *forbid him to breathe through the nose or to swallow* [author's italics], and give a substantial dose of morphia. Only by mouth breathing and a complete cessation of swallowing can the bleeding area be given the necessary and almost infallibly haemostatic rest."

I always use this method first of all, and it is nearly always successful. Later on, and when the bleeding has stopped, a search can be made for the bleeding point. In my experience, heroics are only required for the difficult posterior gushers occasionally encountered.—I am, etc.,

Sonning Common, near Reading. P. M. R. HEMPHILL.

REFERENCE

[1] *University College Hospital Magazine*, 1933, **18**, 117; reprinted in *Collected Papers of Wilfred Trotter*, London, 1941, p. 10.

SIR,—I was very interested in Dr. Humphrey Osmond's letter (*Journal*, April 12, p. 891) about the excellent cork-between-the-teeth treatment of epistaxis which he ascribes to the late Mr. T. B. Layton. In my old hospital (U.C.H.) the method was attributed to the late Mr. Wilfred Trotter. I am not intending to dispute priorities, but only to suggest that a method at once so simple and so ingenious can only have been devised by great men, such as these two.—I am, etc.,

London, S.W.1. PETER DELLER.

Tuberculosis and Alcoholism

SIR,—For a considerable time past we have been interested in a definite relationship between tuberculosis and alcoholism. The biochemistry that seems to make the alcoholic different from others may also be present in tuberculous patients. A trained nurse, a recovered alcoholic, who has had many years' experience with tuberculous patients has repeatedly observed, and we have confirmed it, that those tuberculous patients who are alcoholics are very prone to develop a peculiar psychotic reaction to streptomycin therapy. We would very much like to contact any person interested in this problem.—We are, etc.,

S. J. MINOGUE.
F. J. KYNEUR.

195, Macquarie Street, Sydney, Australia.

Polio Vaccination

SIR,—Many doctors are at present receiving poliomyelitis vaccination, and rightly so, since we are known to be about eight times more likely to die of poliomyelitis than average.[1] The following figures are taken from your article (*Journal*, March 15, p. 637) on "Occupational Mortality," based on the *Registrar-General's Decennial Supplement* covering the years 1949–53.

Eight medical practitioners aged 20–64 died of poliomyelitis where only one death would have been expected. Another fact, to which less publicity has been given, is that seven members of the legal profession also died of poliomyelitis where only one death would have been expected. It does not seem to be either logical or in accord with the standards of our profession to administer the vaccine to ourselves while denying it to the lawyers.—I am, etc.,

Lowestoft. MICHAEL CARTER.

REFERENCE

[1] Doll, R., and Hill, A. Bradford, *Brit. med. J.*, 1957, **1**, 372.

Obituary

J. T. KYLE, T.D., M.B., F.R.C.S.Ed.

Dr. J. T. Kyle, who was in general practice at St. Helens, Lancashire, for thirty years, died on March 27 at his home at Ballymena, Co. Antrim, where he had been living in retirement. He was 68 years of age.

James Taylor Kyle was born at Ballymena and was educated at the Ballymena Academy and at the Queen's University of Belfast, where he graduated M.B., B.Ch. in 1912. He served in France during the first world war, and on his return obtained the F.R.C.S.Ed. in 1920. In the following year he settled in general practice at St. Helens, and found that his special training in surgery was a very satisfying outlet to his energy and skill. In spite of the demands of a busy general practice, he accomplished a tremendous amount of surgical work of a very high standard, most of it in an honorary capacity. He was consultant surgeon to the Rainhill Mental Hospital, and surgeon to the St. Helens Hospital and to the Newton-in-Makerfield War Memorial Hospital. His activities, however, were not limited to his practice and surgical duties, since he became medical officer to the fifth battalion South Lancashire regiment, Territorial Army, and part of his holiday was spent annually at the Territorial Army camp, an event he looked forward to with great keenness. In 1938 he was given the command of the 166th Field Ambulance with the rank of lieutenant-colonel, but he had to relinquish his command soon after the outbreak of the second world war owing to his health. However, he was able to carry on through the war with his usual zest, until he retired in 1950. He was awarded the Territorial Decoration for his services in 1938. He was an active member of the B.M.A., and was chairman of the St. Helens Division in 1929–30. His contributions to discussions were always to the point and appreciated by his colleagues. A keen sportsman, he was a first-class shot and an expert angler. He is survived by his widow and one son, who joined him in the practice in 1947.—R. M. J.

R. S. GLENNIE, M.R.C.S., L.R.C.P., F.P.S.

Mr. R. S. Glennie died suddenly in the garden of his home at Wadhurst, Sussex, on March 30. He was 66 years of age.

Born at Fraserburgh, Aberdeenshire, in 1892, the son of a farmer, Robert Stephen Glennie graduated in chemistry, later becoming chief lecturer in pharmaceutics at the Royal Technical College, affiliated to Glasgow University. While teaching chemistry he decided to become a doctor, and entered St. Thomas's Hospital for his medical training in 1922. Appointed prosector for the Royal College of Surgeons of England and the University of London in 1925, he qualified M.R.C.S., L.R.C.P. in 1926. He was then engaged in general practice in south-west London until 1930, during which period he held the posts of clinical assistant in the throat department at St. Thomas's Hospital and registrar at the West London Hospital. Mr. Glennie spent some time as a postgraduate in Vienna, studying the diseases of the ear, nose, and throat, under Professors Neumann, Hajek, and Hirsch. On returning to England he was appointed assistant surgeon in 1932 to the Metropolitan Ear, Nose, and Throat Hospital, London; in 1936 he became senior assistant surgeon. At that time he was acting as assistant to Sir James Dundas-Grant and later took over his Harley Street practice. For nine years he was deputy consulting laryngologist and otologist to the Oldchurch Hospital, Romford. In 1945 he was appointed ear, nose, and throat surgeon to the Homoeopathic Hospital, Tunbridge Wells. From that time until 1954 he divided his energies between the Metropolitan Ear, Nose, and Throat Hospital in London, Harley Street, and Tunbridge Wells, where he

also had a consulting practice. He was honorary consulting ear, nose, and throat surgeon to the Buchanan Hospital, Hastings, and ear, nose, and throat consultant to the Ministry of Pensions, south-eastern area. In 1950 he was elected a Fellow of the International College of Surgeons. After retiring from London he continued at the Homoeopathic Hospital, Tunbridge Wells, until 1956, and at the time of his death was still engaged in private practice in Tunbridge Wells. For his recreations he turned to fishing, shooting, gardening, and chess, and never lost his interest in farming. He leaves a widow and one son, who is practising medicine in Montreal.—I. J. F.

N. J. BODKIN, M.B., B.Ch.

Dr. N. J. Bodkin died at his home at Southfields, London, on March 31 at the age of 57.

M. D. N. writes : Born in Galway, Nicholas John Bodkin graduated M.B., B.Ch. at the National University of Ireland in 1925. Then, after experience as senior medical officer at the Central Hospital, Galway, and in the East End of London, he settled in general practice in Southfields in 1931. He soon became one of the best-known practitioners in south-west London, while his patients valued his efficiency, cheerfulness, and hard work. Despite his busy life, he served for a time on the old local medical committee. During the second world war, when he was overworked owing to the absence of his partner on active service, he gave an outstanding example of fearless and cheerful service in charge of a mobile unit in the civil defence of Wandsworth. For many years he acted as medical officer to pilgrimages to Lourdes. Owing to failing health he had to give up his golf in recent years, but he still retained his great interest in Rugby football, at which he had represented his university college with distinction. It is a remarkable fact that "Bod" was one of the seventh generation of Bodkins in the medical profession. His requiem mass, presided over by the Bishop of Southwark in a full church, was attended by professional colleagues from all over London. Dr. Bodkin's gaiety of spirit was infectious and his kindness and generosity were proverbial. We shall not look upon his like again. He is mourned by a host of patients, friends, and colleagues, and the sympathy of all is extended to his widow and three children, as well as to his three partners.

HÉLÈNE NORRIS, M.D., L.M.S.S.A.

Dr. Hélène Norris, who was in general practice in the West End of London for many years, died on April 8 after a long illness.

D. C. N. writes: Hélène Rathouse was educated in Geneva, where, after graduating M.D. in 1914, she served as intern in the surgical clinic of Professor Girard. Later she studied neurology in Paris under Professor Soukes, and achieved some success in the treatment of war neuroses, especially hysterical contractures. Her sympathetic temperament and robust common sense often enabled her anxious patients to regain insight and self-control. She spent four happy and useful years in charge of the Maisons Américaines de Convalescence at Arromanches, a haven of refuge for children from the war-devastated areas of Belgium and northern France, including many with tuberculosis and nutritional disorders. During this period she came into contact with members of the British Forces stationed in France, and conceived an admiration for the British and their way of life, so that in 1921 she came to London to study for an English diploma. This she gained in the following year, after study at Charing Cross Hospital and with the aid of coaching (in French—for she spoke hardly any English) from Dr. D. C. Norris, who had been himself a student in the Paris hospitals. In 1923 she and Dr. Norris were married, and, after a few years of residence in the City of London, they moved to Portland Place, where she soon established herself as a general practitioner, and assisted her husband in his medico-legal work. She never had a large practice, greatly preferring to cultivate her patients as friends. It was no uncommon thing for her to spend an hour or more with a single case, discussing quietly all kinds of personal problems, by no means limited to medical matters, and giving detailed advice on diet, work, holidays, and all the thousand and one factors concerned with the welfare of her patient. Many a time a patient has left her consulting-room with a light heart, having discovered for the first time a doctor who seemed to have unlimited time to listen, and who was ready to help at every point in solving a problem. She made proper use of modern remedies, but never fell into the error of thinking that these offered any short cut to success in treatment, or reduced the need for the most careful examination and the most thorough general management of the patient's life so as to secure the best results from treatment. In 1946 she herself underwent a major operation, from which it was not to be expected that she would survive more than five years, but in fact she resumed active practice, and kept reasonably well for ten years before she had again to undergo an operation for recurrence of the condition. Again she rallied to a remarkable degree, and it was only in the last fortnight of her life that the disease got completely out of hand. She had known for years what to expect, and faced the situation with quiet courage and a smile, never allowing her personal feelings to interfere with her work as long as she had strength to carry on. Always glad to renew old friendships in Geneva and France, she was a founder-member and one-time president of the Geneva University Club. She loved to entertain people who had worked with her abroad and who were visiting this country, and to visit them in turn during motor tours of the Continent—an annual event before the second world war. She will be sadly missed by those patients who have profited from her wise advice, which embodied the highest traditions of general practice. She is survived by her husband and by one son, a medical student, who spent a vacation course in the University of Geneva last summer.

D. L. LITTLE, M.B., Ch.B.

Dr. D. L. Little, who had practised in Dudley for over twenty years, died earlier this month. He was 49 years of age.

Douglas Leigh Little was born on October 21, 1908. From Glasgow High School he went on to Glasgow University, graduating M.B., Ch.B. in 1932. During his academic years he took an active part in the athletic club, obtaining his "blue" for hockey and occasionally playing in the university golf team. He was chosen on several occasions for the Scottish hockey final trials but was always second choice for the national team. After resident posts in the Royal Hospital for Sick Children and Eastern District Hospital in Glasgow, he, like so many Scots before him, travelled south across the Border and never regretted it. At first an assistant in West Bromwich in 1934, he joined Dr. V. Gray Maitland in Dudley in 1935 as a partner. A keen Territorial, he left practice at the outbreak of war as medical officer to the 119 Field Regiment, Royal Artillery, serving with them in England and Northern Ireland. Later he served as senior medical officer in troopships, ending his service in 1945 as lieutenant-colonel. On his return to Dudley he quickly regained his practice and was soon in a position to take on a partner. As a supporter of the British Medical Association, he took an active part in local discussions before the National Health Service was established. He represented the Dudley Division at Annual Meetings from 1947 until 1951 and was chairman of the Division in 1953–4. An enthusiastic sportsman, he had represented Staffordshire at hockey before the war, but later he concentrated on golf and was captain of the Enville Golf Club in 1952. Despite the cares of a busy practice he was a member of the Dudley executive council and chairman of the local ward of the Conservative party. Widely

respected for his forthright views and robust sense of humour, he never lost the old-fashioned sense of responsibility towards his patients and was unflagging in his care of them. His final illness, a relic of previous attacks in childhood and adult life, was borne with never-failing good humour and patience, and his passing was peaceful. Douglas Little earned and retained the respect of his colleagues and patients, and his friends will not easily forget him.

In 1937 Dr. Little married Dorothy Round, the then reigning Wimbledon ladies' tennis champion, and to her and their two children, one of whom is studying medicine at his father's university, our sincerest sympathies are extended.—W. N. M.

HARRY SCHOLEFIELD, M.B., Ch.B.

Dr. Harry Scholefield, who was in general practice at Altofts, Normanton, Yorkshire, died on April 10. He was 81 years of age.

Harry Scholefield was born on October 5, 1876, and was educated at Owens College, Manchester, and at the Victoria University of Manchester, where he graduated M.B., Ch.B. in 1900. After graduation he held the appointment of junior house-surgeon at Bury Infirmary, and was then assistant medical superintendent at Paddington Infirmary for a few years before he settled in general practice at Altofts.

N. S. T. writes: Dr. Harry Scholefield practised in Altofts, Normanton, for 50 years until very shortly before his death. He served that industrial and rural area with great devotion and was honoured by his fellow practitioners, who appreciated his absolute integrity, ethical approach, and his determination to "keep modern." His patients always knew that in him they had a friend who would see that they received the best care and treatment at all times. He was chairman of the Wakefield Division of the British Medical Association from 1928 to 1930 and served on the executive committee for many years. His long association with St. John Ambulance work at the local collieries resulted in his being appointed a Serving Brother of the Venerable Order of St. John of Jerusalem in 1939, and 10 years later he was raised to the rank of Officer Brother. For very many years he was medical officer of health for his rural district. He was very interested in cricket and bowls, and did much to foster these games in his village. His daughter was in practice with him as a partner and now succeeds him.

A. GRIFFITH-WILLIAMS, M.R.C.S., L.R.C.P.

Dr. Arthur Griffith-Williams, who was in general practice in the Mattishall district of Norfolk for many years, as was his father before him, died on April 16. He was 70 years of age.

Arthur Griffith-Williams was born at East Dereham on May 1, 1887, the son of Dr. W. H. Griffith-Williams, and was educated at Haileybury and Trinity College, Cambridge. Going on to the London Hospital, he qualified M.R.C.S., L.R.C.P. in 1913, and then held the resident appointments of surgical officer and house-physician at the Norfolk and Norwich Hospital. During the first world war he served as a captain in the R.A.M.C., being attached to the 47th Casualty Clearing Station. When his father died in 1917 he was released from the Army, and took over the Mattishall practice. During the second world war he acted as medical officer to an R.A.F. station. He retired from practice in 1949, after a breakdown in health.

C. S. T. writes: By the death of Dr. Arthur Griffith-Williams, formerly of Mattishall, another fine old country doctor passes from the Norfolk scene. He and his father before him devoted a total of 64 years to the service of their scattered patients. Only those striving to follow in their footsteps can appreciate the depth of the sorrow it has caused to so many of his old patients. They will no more chance to meet him on The Walk on market-day, nor help him when his car breaks down yet again in their village, nor stand outside his waiting-room on a summer evening and talk about his garden. The long hours of work for scant material reward and the care he gave to his patients, and all that that implies, are still the lot and the privilege of the country doctor: his reward lies in the gratitude and love of the most humble patient. "Dr. Billy," unassuming, accessible, and gentle, had that reward in brimming measure. Our sympathy goes out to his widow and daughter, who is a radiographer at Colchester Hospital.

ELSIE COOPER, M.B., Ch.B.

Dr. Elsie Cooper, who had been in general practice in Birmingham and also a part-time member of the staff of the Birmingham public health department, died in hospital in Birmingham on April 17. She was 64 years of age.

Elsie Thomson Douglas Robson was born on September 17, 1893, and studied medicine at Edinburgh University, where she graduated M.B., Ch.B. in 1924. After graduation she gained experience in the eye department and gynaecological ward of Edinburgh Royal Infirmary, and in 1926 she settled in general practice in Birmingham. In the following year, and while still in general practice, she joined the staff of the Birmingham public health department as a part-time medical officer and continued in this capacity until 1942, when she was appointed a full-time medical officer for the duration of the second world war. During that period she gave yeoman service to the city's day nurseries, where at one time as many as three thousand children were being cared for. She returned to part-time work in 1945 and finally left the public health department in 1948. She married in 1930, and her husband survives her.

E. M. N. writes: Dr. Elsie Cooper was an enthusiastic and active member of the Medical Women's Federation, and was on the local committee until a year ago. She served as secretary for five years and also for one year as president, and was constantly endeavouring to recruit new members. Her quiet Scottish humour illumined many a difficult situation in her work. She had the rare gift of appearing to do very little and in fact accomplishing very much. In her last illness her quiet courage in facing the inevitable end was an inspiration to her friends, who will remember her with the warmest affection.

G. W. RAKE, M.B., B.S., F.A.C.P.

Dr. G. W. Rake, scientific director of the international division of the Olin Mathieson Chemical Corporation, died at Princeton Hospital, New Jersey, U.S.A., on April 20. He was 53 years of age.

Geoffrey William Rake was born at Fordingbridge, Hampshire, and received his medical training at Guy's Hospital. Qualifying M.R.C.S., L.R.C.P. in 1927, he took the London degrees of M.B., B.S., with honours, in the following year. After resident posts at Guy's Hospital he went to Baltimore in 1931 to take up an appointment at Johns Hopkins Hospital. Later he joined the staff of the Rockefeller Institute of Medical Research in New York, and then spent a year as a research associate at the Connaught Laboratories in the University of Toronto. For some years he was research professor of microbiology in the University of Pennsylvania, and he became scientific director of the international division of the Olin Mathieson Chemical Corporation about two years ago. One of the original members of the virus and rickettsial study section of the Public Health Service in the United States, he was the author, jointly with Dr. Harvey Blank, of *Viral and Rickettsial Diseases of the Skin, Eye, and Mucous Membranes of Man*, a short but comprehensive textbook on virus diseases which was published in 1955. Dr. Rake had conducted a good deal of research on virus diseases, and had visited India, Mexico, and China to advise on research programmes in those countries.

HECTOR CAMERON, M.D., LL.D., F.R.C.P.

The obituary of Dr. Hector Cameron was published in the *Journal* of April 12 (p. 893).

Dr. DONALD PATERSON writes from Vancouver, B.C.: Hector Charles Cameron was my second son's godfather, and we saw a great deal of him. I never tired of his stories—he was one of the best story-tellers I have ever known. He was the first person to point out to me the tendency for a doctor to be accusing and aggressive to a parent and in this way bring out aggressiveness in that parent toward the doctor. His theory of always giving the mother the benefit of the doubt and assuming that she was right and trying to do her best according to her own lights was new at the time I first met him, and it opened up new fields for me and made for me many friendships that I would otherwise have missed. His ability to understand the child's mind and its capacity to take colour from its surroundings was another of his great contributions. He was the first to say: "Give a child a bad name and he will try to live up to it—give him a good name and he will do likewise." Praise is the thing—how often he preached that. Although he will be remembered for his *Nervous Child*, nevertheless his lecturing and writings in the current medical journals had a profound influence on paediatrics in my early days.

J. P. SEMPLE, M.B., Ch.B., F.R.C.S.Ed.

The obituary of Mr. J. P. Semple was printed in the *Journal* of April 19 (p. 947).

D. R. L. S. writes: John Semple's sudden and untimely death is a shattering blow to his many friends. I had the privilege of being his colleague for a number of years, as well as a close friend. He was a quiet man who took a lot of really getting to know. However, when you did get to know him you found him to be one of the most kind and generous of men that could ever be met. I have never known or heard of him to be unkind to a patient or to any of the staff who worked under him. He was a great diagnostician, and as sound and as speedy a surgeon as I have ever seen. His death has meant the loss to surgery of a top-class man in his prime, and to Doncaster particularly the loss of one who will be more than usually difficult to replace. One of "God's Good Men" has passed on.

Medical Notes in Parliament

HOUSE OF LORDS

Legal Aid Scheme

Viscount ELIBANK drew attention in the House of Lords on April 22 to the observations of Mr. Justice Roxburgh in the Chancery Division, on the need for stopping a legally aided case that was being boosted by false evidence,* and asked if the Government would consider introducing into the legal aid scheme such changes as would enable that to be done. The Judge had also said that the effect in the case in question (in which judgment was given for the defendants) was that the costs would be shared between the defendants and the taxpayer.

The LORD CHANCELLOR replied that the Law Society's committees who investigated applications for legal aid had acted entirely correctly throughout. The Judge had pointed out that the issue raised was how it was possible to stop a legally aided case when things turned out contrary to expectations. The regulations provided that the responsible committees should discharge the certificate of legal aid on information coming to their knowledge which led them to consider that there were no longer reasonable grounds for the proceedings, or that in the particular circumstances it was unreasonable for legal aid to continue. It was open to anyone who thought a case should no longer be legally aided, including the other side, or the solicitors or counsel acting for the legally aided person, to give what information they had to the committee. No information reached the appropriate committee in this case. He appreciated that the consequences to the opposite party could be severe, but, despite further consideration of the feature of the legal aid scheme under which a successful opponent in a legally aided case often had to bear the whole burden of his costs himself, he was still unable to commend any method under which the position could be alleviated.

*See *British Medical Journal*, April 26, p. 1009.

Tribunal Hearings in Public

The House of Lords began the committee stage of the Tribunals and Inquiries Bill, which gives effect to some recommendations of the Franks Committee, on April 22. Lord MILNER OF LEEDS moved a new clause providing that all hearings by tribunals or inquiries should be held in public unless the Lord Chancellor in a particular case certified that it would be contrary to the national interest. Lord DENNING said that, although there should be exceptions, if tribunals were to be brought within the judicial system as the Franks Committee recommended, it should be laid down by statute as a general principle that all hearings should be in public, subject to the provisions of any procedural rules that might be prescribed after consultation with the Council on Tribunals which the Bill would establish.

Viscount HAILSHAM, Lord President of the Council, argued the proposed clause would put on the Lord Chancellor the burden of saying whether hearings of tribunals of which he had no personal experience were to be held in public or private, by reference to cases of which he had no knowledge; and that his criterion in doing so should be the public interest and not justice, both of which were dangerous propositi. He preferred the Franks recommendation: "Hearings before tribunals should be held in public except in cases where: (i) considerations of public security are involved; (ii) intimate personal or financial circumstances have to be disclosed; or (iii) the hearing is a preliminary investigation of a case involving professional capacity and reputation." The object in this Bill had been to protect the individual, and not the public. He pointed out that the tribunals enumerated in the Schedule to the Bill included, for example, investigations by the Service Committee under the Health Service, in which the whole reputation of a doctor might be brought into question without his necessarily coming before the General Medical Council. Nobody would ask for that kind of inquiry to be held in public. Another example was the independent schools tribunals. Broadly speaking, it was right to propose, as the Government did, to leave it as one of the first duties of the Council on Tribunals to decide to which category the ordinary rule of public hearing should apply. That was much more in accordance with the Franks recommendation, and much more practical, than the proposed clause. The new clause was, by leave, withdrawn.

ADJOURNMENT DEBATES

Morphine at Port Medical Centres

The supply of morphine for use in port medical centres was asked for by Mr. J. CALLAGHAN (Cardiff, South-East, Lab.), on April 24. His appeal was made in consequence of an accident at Cardiff docks last October, when a ship's officer had his leg caught in the noose of a wire hawser and torn off. Because the nursing sisters who staffed the medical centre were not allowed morphine they could do nothing to relieve the man's agony, and he had to be got ashore and taken three miles to the hospital.

He recalled that in 1950 and 1953 the National Dock Labour Board had made representations to the Home Office, but had been refused supplies. The first reason given for the refusal was that the Government had undertaken that the use of morphine should be under strict supervision and control. With that he agreed, although he hoped it would not be suggested that there were not adequate

facilities at port medical centres. The second reason given was that "consultation with the medical profession in the past has shown that a weighty volume of medical opinion supports this principle." This he did not believe. He had asked for the views of the Cardiff branch of the B.M.A., but received no reply, so obviously they did not feel strongly about it one way or the other. Dr. Macrae, secretary of the B.M.A., in a full letter had told him that the B.M.A. had made representations to the Home Office in 1955 and 1957 asking that supplies of morphine should be made available on a wider basis in industrial places where there were medical centres, though not raising the question of port medical facilities. The Royal College of Nursing took the same view. Being unable himself to find this weighty volume of medical opinion he had asked the Home Secretary (on March 20), "What is the weighty volume of medical opinion which has led him to deny the use of an emergency supply of morphine" to port medical centres; and had received a skilful but evasive reply that "It is generally considered desirable that these [drugs] should be administered by or under the direct supervision of a qualified medical practitioner." He maintained that properly controlled conditions were to be found at port medical centres, staffed by State-registered nurses, and that common humanity demanded that the need should be met.

Vice-Admiral J. HUGHES-HALLETT (Croydon, North-East, Con.) said the question was raised indirectly in a more general form in an amendment he moved at the request of the B.M.A. during the committee stage of the Opticians' Bill. That was intended to prohibit the supply of dangerous drugs to ophthalmic opticians. One of the objections was that it would have prevented them from being able to use pain-killing drugs, for example, in removing a splinter from an eye after an accident, or cases of that kind. That was one of the reasons why the amendment was withdrawn. It seemed hard to defend the anomaly that trained nurses at medical centres standing by to deal with accidents should be forbidden to administer morphine.

Mr. D. RENTON, Under Secretary, Home Office, first made two general points. Although morphine did good by relieving pain, it also did harm by masking symptoms that might be important in diagnoses. That was one reason why it had been generally accepted by the medical profession that wherever possible a doctor should be present when morphine was administered. Secondly, the country was comparatively free from drug addiction because of the strictness and efficiency of the system of control, based on the general principle that no one should be in possession of dangerous drugs unless authorized by law.

There was no evidence that the circumstances of docks in general were such as to justify a broad exception to the general principle. He could not therefore give Mr. Callaghan the answer he sought. He was, however, arranging for the matter to be urgently considered. In making those inquiries the fullest weight would be given to humanitarian considerations. It would be necessary to consult other departments and the various authorities and professional bodies concerned. If any extensive exception was to be made it might be found that fairly complicated administrative arrangements for licensing and inspection would be necessary. Mr. Callaghan thanked him for that, and added that according to his information there were 26 ports which had medical centres, and there were 67 State-registered nurses employed, so it would not be a very big exercise if they had to be scheduled and inspected.

ANSWERS TO QUESTIONS

More Polio Vaccine Ordered

The MINISTER OF HEALTH was questioned again about supplies of poliomyelitis vaccine on April 28, and in addition to telling M.P.s that a further quantity of American Salk vaccine was to be bought he promised further information for the debate on May 1.

Mr. M. EDELMAN (Coventry, North, Lab.) asked the Minister for a statement on the adequacy of the supplies of antipoliomyelitis vaccine likely to be made available this summer. Mr. B. JANNER (Leicester, North-West, Lab.) asked why the Minister did not order sufficient of the vaccine from North America in time to allow for the testing period to be completed.

Mr. WALKER-SMITH replied that batches of vaccine from the two British manufacturers which were distributed to local health authorities last week totalled over half a million doses, and a batch of Canadian Salk vaccine of half a million doses would be distributed within the next few days. Over eight and a half million doses of vaccine would then have been distributed in Great Britain since the start of the scheme, four and a half million of them since the beginning of this year. Further vaccine should be distributed in May. These supplies would enable local health authorities to make good progress with vaccinations. In addition to what was already in the pipeline he was arranging for the purchase of a further quantity of American Salk vaccine in addition to the 7,800 litres and replacements previously ordered from Canada and the U.S.A., and would give further details to the House on May 1.

Mr. EDELMAN welcomed the energy and improvisation of the Minister in repairing the breakdown of the programme, but suggested that even the most energetic authorities could only inoculate at the rate of 3,000 a week. Mr. WALKER-SMITH said that he did not accept that there had been any failure. There had been interruptions in the anticipated supplies. These he was engaged in repairing and supplementing. He did not think Mr. Edelman's assumption of the capacity of local authorities was right. He was confident that when there were larger batches of vaccine, as there presently would be, the programme could be accelerated considerably.

Mr. JANNER said the Minister had been asked months ago why he was not purchasing adequate supplies from North America. Had he then ordered the requisite quantity he would have been able to meet all requirements. The Minister had been scandalously negligent. Mr. WALKER-SMITH said that when the original importation of Salk vaccine was arranged the Ministry were acting on the advice of the Medical Research Council that it should be regarded as a temporary measure until adequate British supplies became available. There was no reason at the time to foresee an interruption of British supplies on the scale that had happened. In any event the stocking of vaccine at that stage would have been inappropriate, since it was not then possible to estimate its acceptability, and its potency was not permanent.

Dr. EDITH SUMMERSKILL (Warrington, Lab.), who complained that the statement made by the Minister on April 21 did not correspond with statements by the director of the Connaught Laboratories, which was the source of Canadian supplies, or with statements from the U.S. Public Health Service, asked if the Minister could say whether before June 1 five million who had registered would have had two inoculations. Mr. WALKER-SMITH said he hoped that might be the case, but there were a good many unpredictable factors.

No Final Date for Registration

There was a considerable programme ahead, Mr. WALKER-SMITH also stated, and it was a little difficult to speak in terms of a precise date for completion. Registration was a continuing process, and he did not intend to place a final date on registration.

The Minister, in a further reply to Mr. Edelman, said there would be a good many technical considerations involved before French or other sources of supply could be brought into use, which did not arise in the same sense with U.S. or Canadian sources.

£1,750,000 Cost So Far

Mr. G. CHETWYND (Stockton-on-Tees, Lab.) asked what was the cost of the vaccine purchased to date, and what was

the total estimated cost to complete the programme. Mr. WALKER-SMITH replied that the total cost of supplies distributed to date in Great Britain was approximately £1¼m.: between one-third and one-quarter of this amount was paid for imported supplies. As registration was a continuing process he could not as yet estimate with precision the cost of the completion of the programme.

Mr. CHETWYND asked for an assurance that the availability of the vaccine would not be held up by a dollar shortage or lack of production resources at home. Mr. WALKER-SMITH told him there was no particular difficulty with regard to money. The estimates for 1958–9 showed a figure of £2m., equivalent to 10 million doses. If more should be necessary he was sure the House would be sympathetic to a supplementary estimate.

Medway Outbreak

Mr. A. BOTTOMLEY (Rochester and Chatham, Lab.) asked the Minister for a statement about the outbreak of poliomyelitis in the Medway towns area. Mr. BURDEN (Gillingham, Con.) asked what advice regarding special allocation of vaccine had been given. Mr. WALKER-SMITH replied that three cases of poliomyelitis had been notified in Gillingham since the week ending April 12, but there had been no recent notification either in Chatham or in Rochester. He was advised that vaccination was not generally regarded as a suitable emergency method of checking a local outbreak of poliomyelitis, and no special allocations of vaccine were therefore made in such circumstances. Mr. BOTTOMLEY said there had been outbreaks in the Medway towns for some time past, and a special allocation of vaccine should have been made much earlier. Mr. WALKER-SMITH pointed out that the system was to distribute vaccine in relation to the number of registrations, and he thought that was probably the best procedure. Mr. F. BURDEN (Gillingham, Con.) said that considerable anxiety had been caused in the Medway towns by a reference in the national Press to the father of a boy who died recently and who, it had been said, had blamed the Health Service for the boy's death. The father had since denied ever having made such an allegation. Mr. WALKER-SMITH said he was grateful to Mr. Burden, and to the man. It was unhappily a fact that one or two of the national newspapers appeared to have behaved with less than the traditional sense of responsibility which they expected of the national Press.

Drugs for Private Patients

Lieutenant-Colonel W. H. BROMLEY-DAVENPORT (Knutsford, Con.) asked the Minister whether he was yet in a position to state the result of his department's discussions with the British Medical Association about the provision to all private patients free of charge, other than the prescription charge, of a selected list of drugs; what would be the estimated cost of allowing these drugs to private patients; and whether consideration would be given to amending the National Health Service Act on these lines. Mr. WALKER-SMITH stated that the discussions, which related to the supply of all necessary drugs and not a selected list, and were of a purely exploratory nature, were still in progress. Any estimate of cost would be highly speculative because the number of private patients was not known.

U.N. Committee on Atomic Radiation

Mr. SWINGLER asked the Prime Minister who were the United Kingdom representatives on the United Nations Scientific Committee on the Effects of Atomic Radiation, and if he would ask the Committee to hasten the publication of its report, in view of the dangers of increasing radioactivity from nuclear tests.

Mr. MACMILLAN told him that Dr. E. R. Pochin, director of the Medical Research Council's Department of Clinical Research, University College Hospital Medical School, was the United Kingdom representative. Dr. W. G. Marley, head of the Health Physics Division of the Atomic Energy Research Establishment, Harwell, was his alternate. When the committee was set up by the United Nations it was asked to report by July of this year. He understood that they had nearly completed their work, and that there was every reason to hope that the report would be published on time.

Medico-Legal

MENTAL HOSPITAL FATALITY

ATTACK BY PATIENT

[FROM OUR LEGAL CORRESPONDENT]

At the inquest held on January 16 before the Leeds coroner on Mr. George Henry Hindle-Smith, the following facts were given in evidence.

Mr. Hindle-Smith, then aged 84 and a frail old gentleman, a retired paper merchant and agent, was certified in September, 1956, and had since that date been an inmate of Scalebor Park Mental Hospital, in Wharfedale, suffering from senile dementia. In 1944 Ronald Thomas Hallas was first admitted to Scalebor Park, and apart from a year when he was in a mental hospital in Dumfries at his own request he also had been in Scalebor Park ever since. He suffered from paranoid schizophrenia, and was said by Dr. James Valentine, the physician superintendent, to have been in a state of gross mental disturbance during the whole period. He had delusions of persecution, and imagined that voices told him to do various things. One voice he referred to as "the Detective upstairs." He was at times noisy, abusive, and threatening, and occasionally violent, generally towards members of the staff.

"I've Knocked Him Right in His Head"

On December 9, 1957, a staff nurse saw Mr. Hindle-Smith walking slowly and unsteadily down one of the hospital corridors and saw him pass Mr. Hallas, who without any word or warning struck him a fairly sharp blow under the right shoulder and knocked him down. When the nurse remonstrated with Mr. Hallas he replied, "I've knocked him right in his head." Mr. Hindle-Smith, who sustained a fractured femur, was transferred to Leeds General Infirmary, where he died on January 14 of bronchopneumonia consequent upon the fracture.

On January 15 Detective Inspector Earnshaw saw Mr. Hallas in Scalebor Park, and without telling him who he was said he was interested in the incident when Mr. Hindle-Smith was knocked down. The only coherent answer was that "the Detective upstairs hit him through Hallas." He concluded that Mr. Hallas was out of his mind.

Dr. Valentine, who on the afternoon of the incident had been quite unable to get any account of it from Mr. Hallas, said that by reason of the latter's mental illness he would have been quite unable to form any rational intent to harm the old gentleman. It was likely that he had acted on the spur of the moment. He may have thought that Mr. Hindle-Smith was more insane than himself and struck him with the intention of helping him by knocking some sense into him, as was suggested by his answer to the nurse directly afterwards. Possibly he thought "the Detective upstairs" said, "Hit him in the head to do him good." At the time of the blow he was suffering from a disease of the mind, and if he knew what he was doing, which was doubtful, he would not have thought it wrong and would have done the same even with a policeman standing at his elbow.

Having thus brought the situation squarely within the McNaughton Rules, Dr. Valentine went on to say that at the

time of the inquest Mr. Hallas was not able to understand enough to instruct solicitor or counsel or to appreciate the nature of a trial for murder.

The Verdict

In the light of Dr. Valentine's evidence it was clearly impossible for the coroner's jury to return a verdict of murder or manslaughter against Mr. Hallas, and they accordingly returned the only other verdict open to them—namely, "Death by misadventure," which was duly recorded by the coroner.

This case is an example of how very useful an inquest can sometimes be. The evidence of the state of Mr. Hallas's mind having been publicly given and the implications formally recorded in the jury's verdict, it became thereupon unnecessary in the interests of justice to take criminal proceedings, which in the circumstances could not but have been expensive, unedifying in that someone so mad as to be unfit to plead would have had to be submitted to committal proceedings before the magistrates and committed for trial, and futile in that at the trial he must have been found either unfit to plead or guilty but insane. As it was, justice could be done and be seen to be done without Mr. Hallas ever emerging from the shelter of Scalebor Park.

KILLING BY EPILEPTIC

[FROM OUR LEGAL CORRESPONDENT]

On March 26 Brian George Candy, aged 21, was at Winchester Assizes found guilty of the manslaughter of Lynne Diane Wilson, aged 16. He had been charged with her murder, and the defence was one of diminished responsibility by reason of epilepsy (*Daily Telegraph*, March 27).

Candy said in evidence that when he was out walking with the girl he heard her scream, and something hit him or was pressed against the back of his neck, after which he had no memory of what happened until he found her dead.

Dr. Christie, senior medical officer at Winchester Prison, was called for the defence. He said that Candy had been under treatment since March, 1956, for recurrent headaches, sharp pains down the right side of the head, and some stiffness of the neck. He had come to the conclusion that Candy was in the early stages of the onset of epilepsy, and this, although not rendering him insane, affected his powers of understanding and control. An epileptic attack would last a few seconds. In cross-examination Dr. Christie agreed that it would have taken more than a few seconds to strangle the girl, carry her body for some distance, and then remove a ligature from her neck and replace it with one of her stockings.

After the jury had returned their verdict of manslaughter, Mr. Justice Stable said that they had found Candy to be suffering from epilepsy, a disease which had been said to go from bad to worse, and which had such an effect on his mental powers that he could not or did not resist the inclination to strangle the girl. In the circumstances he was a social menace, and the sentence would be imprisonment for life.

Vital Statistics

Smallpox in Cheshire

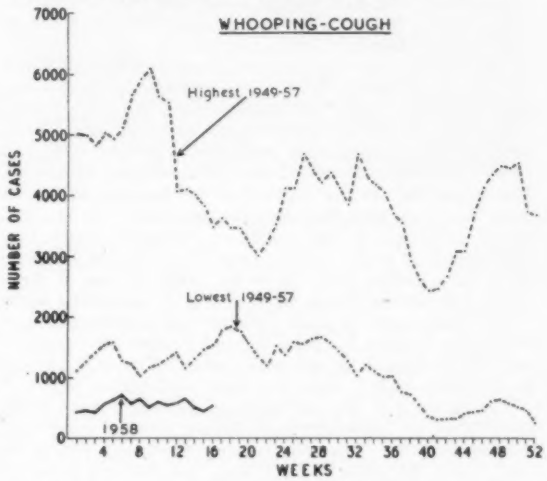
Two more cases of smallpox have been reported from Bebington, Cheshire, since last week. They are the grandmother and 7-year-old sister of the 2-year-old boy who was removed to hospital with the disease on April 14. In both the new cases the disease was extremely modified, and neither was seriously ill. Virological confirmation has been obtained.

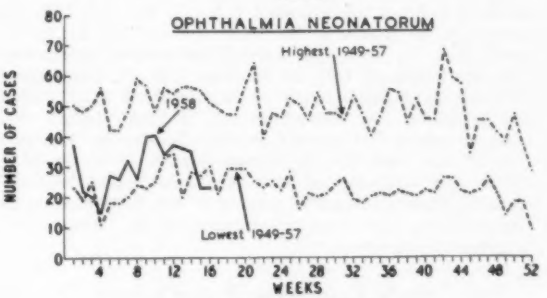
The grandmother had been vaccinated in infancy and was revaccinated with a primary take when the disease was diagnosed in her grandson. She was also given hyperimmune serum then. On April 21 she began running a temperature of 100–101° F. (37.8–38.3° C.), and on April 23 she developed a profuse discrete macular rash which could be felt as well as seen over her trunk. She had a slight rash on legs and arms, but none on her face. On April 24 the rash became morbilliform, and subsequently a few papules and vesicles developed.

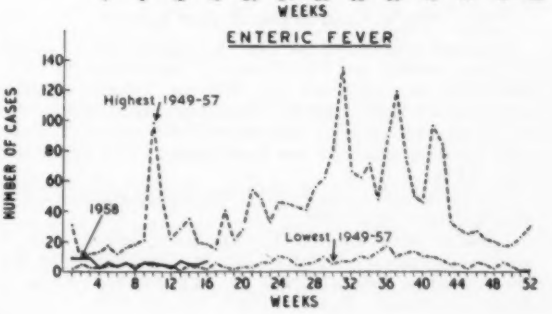
The sister had not been vaccinated in infancy and was successfully vaccinated at the same time as the grandmother. She also received hyperimmune serum. On April 22 she began running a temperature of 101–102° F. (38.3–38.9° C.). By April 25 her temperature had settled, and she then developed a very sparse papular rash.

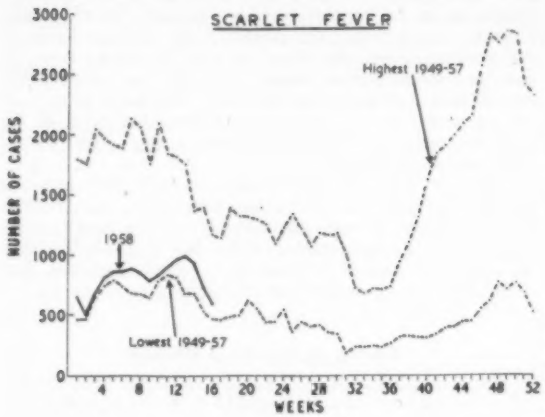
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1949–57 are shown thus - - - - -, the figures for 1958 thus ————. Except for the curves showing notifications in 1958, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Week Ending April 19

The largest variations in the returns of infectious diseases in England and Wales during the week ending April 19 were rises in the number of notifications of 147 for dysentery, from 863 to 1,010, 44 for whooping-cough, from 495 to 539, and falls of 139 for scarlet fever, from 738 to 599, and 29 for acute pneumonia, from 585 to 556.

The number of notifications of measles, 5,057, was 9 fewer than in the preceding week. The largest falls in the incidence of measles were 132 in Hampshire, from 401 to 269, and 138 in Devonshire, from 287 to 149; the largest rises were 163 in London, from 281 to 444 (Islington 178) and 54 in Lancashire, from 462 to 516 (Liverpool C.B. 154). The largest fall in the number of notifications of scarlet fever was 31 in Yorkshire West Riding, from 85 to 54. The largest variations in the trends of whooping-cough were increases of 25 in Lancashire, from 37 to 62, and in Yorkshire West Riding, from 39 to 64. Only 1 case of diphtheria was notified compared with 4 in the preceding week.

The notifications of acute poliomyelitis numbered 19, and these were 6 more for paralytic and 2 more for non-paralytic cases than in the preceding week. The only administrative area with 2 cases was Kent, Gillingham M.B.

The increase in the incidence of dysentery was mainly contributed by Yorkshire West Riding with an increase of 126 notifications. The chief centres of infection during the week were Yorkshire West Riding 280 (Dearne U.D. 65, Sheffield C.B. 48, Huddersfield C.B. 23, Barnsley C.B. 20, Leeds C.B. 19, Bradford C.B. 18, Pontefract M.B. 11, Hemsworth R.D. 11, York C.B. 20), Lancashire 276 (Manchester C.B. 65, Liverpool C.B. 56, Oldham C.B. 54, Chadderton U.D. 18, St. Helens C.B. 11, Lancaster M.B. 10), London 95 (Islington 29, Shoreditch 12, Bethnal Green 10), Gloucestershire 53 (Bristol C.B. 50), Cheshire 48 (Wallasey C.B. 22, Sale M.B. 12), Nottinghamshire 32 (Worksop M.B. 23), Surrey 24 (Richmond M.B. 20), Middlesex 24, Staffordshire 23 (Newcastle-under-Lyme M.B. 10), Warwickshire 23 (Birmingham C.B. 14), and Hampshire 21 (Havant and Waterloo U.D. 11).

England and Wales in First Quarter

The death rate of 14.8 per 1,000 population was 2.6 above the corresponding rate for 1957 and 0.5 below that for 1956. The infant mortality rate was 25.1 per 1,000 live births, which was 0.1 higher than the record low rate of 25.0 for the March quarter last year. But the stillbirth rate of 21.4 per 1,000 live and stillbirths was lower than in 1957 (22.6) and 1956 (23.5).

Live births numbered 190,623, the highest number for a March quarter since 1949.

Neonatal Mortality in 1957.—Deaths of infants under 4 weeks old numbered 11,904, or 16.5 per 1,000 live births, the lowest annual rate recorded in England and Wales.—*Registrar-General's Weekly Return*, No. 16, 1958.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **April 12** (No. 15) and corresponding week 1957.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire	1957 Eng. & Wales	1957 Lond.	1957 Scot.	1957 N. Ire.	1957 Eire
Diphtheria	4	0	1	0		3	0	3	0	1
Dysentery	863	71	203	7	6	1,171	62	295	13	3
Encephalitis, acute	3	1		0		4	0		0	
Enteric fever:										
Typhoid	3	1	0	0		3	1	0	1	
Paratyphoid	2	1	1(B)	0	4(B)	2	0	0	0	
Food-poisoning	112	11	13	1		194	13	12	1	
Infective enteritis or diarrhoea under 2 years				12	18				10	24
Measles *	5,066	281	131	37	8	27,275	2016	339	418	315
Meningococcal infection	24	2	16	0	7	24	2	15	1	1
Ophthalmia neonatorum	23	1	2	0		27	0	5	0	
Pneumonia †	585	44	323	4	3	497	20	102	3	13
Poliomyelitis, acute:										
Paralytic	9	0	2	0	4	22	2	3	0	5
Non-paralytic	2	0				15	1			
Puerperal fever §	244	36	17	1	1	205	46	12	0	
Scarlet fever	738	53	56	24	28	740	56	78	48	13
Tuberculosis:										
Respiratory	458	59	148	14		697	88	313	18	
Non-respiratory	73	5	16	2		89	7	16	5	
Whooping-cough	495	33	31	6	4	2,616	130	292	8	59

DEATHS	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire	1957 Eng. & Wales	1957 Lond.	1957 Scot.	1957 N. Ire.	1957 Eire
Diphtheria	1	0	0	0	0	No comparable figures available.	0	0	0	0
Dysentery	2	0		0			0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0			0	0	0	
Infective enteritis or diarrhoea under 2 years	7	0	2	0	1		1	2	1	0
Influenza	57	1	1	0	1		2	0	0	3
Measles		0	0	0	0		0	1	0	0
Meningococcal infection		1	0				0	0		
Pneumonia	719	65	42	18	8		36	11	12	7
Poliomyelitis, acute	1	0		0	0		0			0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	96	5	12	2	6		6	9	1	2
Non-respiratory		0	6	0	0		2	0	0	0
Whooping-cough	1	0	0	0	1		0	0	0	0
Deaths 0–1 year	336	36	46	8	12		33	23	6	8
Deaths (excluding stillbirths)	11,280	933	783	137	194		732	523	105	185
LIVE BIRTHS	14,710	1319	1149	239	420		1141	926	247	404
STILLBIRTHS	378	27	34				16	20		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Imperial Cancer Research Fund.—Professor G. F. MARRIAN, F.R.S., professor of chemistry related to medicine at Edinburgh, has been appointed director of all the Fund's research. This was announced by Sir CECIL WAKELEY, chairman of the Fund's council, when presenting the report for 1956–7 at the Fund's annual meeting in London on April 29. This appointment anticipates the Fund's considerably expanded future research programme when the new block of laboratories in Lincoln's Inn Fields are erected. Permission to demolish Nos. 44, 45, and 46, Lincoln's Inn Fields was granted in January, and the Fund is now able to make detailed plans. An account of the Fund's research will be printed later.

Wellcome Trust Benefactions.—The Wellcome Trustees have allotted grants for medical research in the Commonwealth totalling £108,630 for the half-year ended March 31. They include grants to the following: (1) Institute of Cancer Research, London University: £40,000 for the cost of including a Wellcome laboratory of pharmacology and experimental chemotherapy in the proposed extension of the Chester Beatty Research Institute. (2) Government of Kenya: Up to £10,000 for the cost of adding a Wellcome research library to the Medical Research Laboratories at Nairobi. (3) Nuffield Department of Surgery, University of Oxford: About £16,500 for the purchase of a Gibbon-Mayo heart pump for use in research on the surgery of the heart. (4) Department of Pharmacology, Sydney University: About £3,000 for a scintillation spectrometer for work with radioisotopes. (5) Department of Pharmacology and Therapeutics, Manitoba University, Winnipeg: £13,000 to provide the stipend of a Wellcome research fellow for six years.

F.R.C.P. and M.R.C.P.—At the quarterly comitia of the Royal College of Physicans of London on April 24, the following were elected fellows of the College:

Dr. P. Kutumbiah (India), Dr. J. O. Mercer (New Zealand), Dr. W. F. Connell (Canada), Dr. J. H. Walters (London), Dr. Shiva S. Misra (India), Dr. F. S. Brien (Canada), Dr. S. Adler (Jerusalem), Dr. T. Simpson (London), Dr. W. Goldie (Leeds), Dr. W. A. Oliver (Norwich), Dr. Elizabeth J. Stokes (London), Dr. J. E. Clarke (Australia), Surgeon-Commander M. A. Rugg-Gunn (London), Dr. C. J. C. G. Hodson (London), Dr. J. L. Pinniger (London), Dr. Ursula James (London), Dr. D. de la C. MacCarthy (Aylesbury, Bucks), Dr. J. P. M. Tizard (London), Professor M. Roth (Newcastle upon Tyne), Dr. A. Thelwall Jones (Liverpool), Dr. W. S. Peart (London), Dr. H. E. de Wardener (London), Dr. D. Stafford-Clark (London), Dr. A. D. Charters (Kenya), Dr. P. H. Davison (Birmingham), Dr. S. C. Gold (London), Dr. M. D. Milne (London), Dr. E. B. Adams (South Africa), Dr. I. C. K. Mackenzie (London), Dr. S. W. Stanbury (Hale Barns, Cheshire), Dr. S. T. Anning (Leeds), Dr. D. H. Collins (Sheffield), Dr. J. S. I. Skottowe (Oxford), Professor C. H. Gray (London), Professor T. McKeown (Birmingham), Professor J. S. Mitchell, F.R.S. (Cambridge), Sir Lindor Brown, F.R.S. (London), Dr. E. Ford (Australia), Sir Hans Krebs, F.R.S. (Oxford).

The following, having satisfied the censors' board, were elected members of the College:

Drs. B. I. Chazan, G. Cohen, G. L. Donnelly, G. H. Failey, Nellie P. Fernando, P. N. Francis, M. Greenberg, C. B. Hatfield, T. D. R. Hockaday, R. D. Hyde, J. H. Jones, G. S. McL. Kellaway, R. S. Kocen, A. Kushlick, P. J. Lachmann, H. Lehmann, E. Lewis, C. Mawdsley, R. J. Mulhearn, M. J. Pritchard, S. B. Rosalki, R. W. Ross Russell, K. F. R. Schiller, S. Shuster, G. Simon, and I. D. H. Todd.

Kathleen Ferrier Memorial.—On April 24 Sir HENRY DALE, O.M., opened the Kathleen Ferrier extension of the radiotherapy department at University College Hospital, London, unveiling there a portrait plaque of Miss Ferrier by Mrs. Mary Gillick, the designer of the Queen's effigy on our coinage. It was Miss Ferrier's idea that after her death a memorial fund should be established to augment the resources of the department where her fatal throat ailment was treated and temporarily alleviated. So far over £15,000 has been collected, and this is being used to provide a cobalt unit with facilities for treatment under increased oxygen tension, extra staff, and extra accommodation. Mr. MYLES FORMBY welcomed the guests on behalf of the hospital. Lord Justice ORMEROD, as one of Kathleen Ferrier's friends, paid tribute to Dr. Gwen Hilton, the director of the department, to the Sister who had looked after Miss Ferrier, and to the hospital. Their treatment had allowed the world two more years of Kathleen Ferrier's singing.

Dr. Sheldon, Freeman of Wolverhampton.—On April 21 Dr. J. H. SHELDON was admitted an honorary freeman of the County Borough of Wolverhampton. He is the first medical

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man to be thus honoured. The picture shows the Mayor of Wolverhampton, Alderman Mrs. R. F. ILSLEY, presenting Dr. Sheldon with a silver casket and the scroll recording the borough council's resolution. The resolution records that Dr. Sheldon came to Wolverhampton in 1921 as physician to the Wolverhampton and Staffordshire General Hospital (now the Royal Hospital) and will be retiring from his appointment as director of medicine there this September. "During this time Dr. Sheldon has achieved international eminence in his great profession," states the resolution, and continues: "The magnitude of his professional attainments has not distracted him from the devoted care of his patients, to whom his great skill and knowledge have been always dedicated."

British Association of Physical Medicine.—The British Association of Physical Medicine held its annual dinner on April 25 at the Royal College of Physicians. The president of the association, Dr. P. BAUWENS, was in the chair. Professor R. PLATT, P.R.C.P., in proposing the toast of the association, said, among other things, that he would like to found a society for the abolition of gloom in medicine, to be known—in these days of initials—as SAGIM. "Today," he said, "we know so much that we no longer need pretend we know everything." Dr. BAUWENS, in reply, reported a satisfactory year's progress in the association's affairs. Dr. HUGH BURT, vice-president of the association, proposed the health of the guests, and Dr. IAN D. GRANT, president of the College of General Practitioners, replied.

Central Midwives Board.—At a meeting of the Central Midwives Board on April 3 Mr. ARNOLD WALKER was re-elected chairman and Professor A. A. MONCRIEFF deputy chairman for the ensuing year.

Assistant Secretary of the B.M.A.—The Council of the British Medical Association invites applications for the post of assistant secretary. Candidates must be registered medical practitioners, of either sex, not over 35 years of age. Further details of the appointment will be found in our advertisement columns (p. 40). The closing date for applications is June 7.

Honorary Degrees at Glasgow.—Among those who will receive the honorary degree of Doctor of Laws of Glasgow University at the Commemoration Day ceremony on June 18 are: Professor JOHN CRUICKSHANK, formerly professor of bacteriology at Aberdeen University; Dr. T. F. FOX, editor of the *Lancet*; Professor ERIK HUSFELDT, professor of clinical surgery, Copenhagen University; and Professor H. A. KREBS, F.R.S., professor of biochemistry, Oxford University.

COMING EVENTS

Moynihan Lecture.—Professor H. ROCKE ROBERTSON, professor of surgery at the University of British Columbia, will lecture at the Royal College of Surgeons on May 6 at 5 p.m. on "Observations on Wound Infection."

"Electrophoresis in Clinical Biochemistry."—Joint meeting of the Association of Clinical Biochemists (Southern Region) and the Society for Analytical Chemistry on May 7 at 7 p.m. at Burlington House, London.

Sir David Wilkie Lecture.—Mr. J. G. MURRAY will lecture at the Royal College of Surgeons of Edinburgh on May 9, at 3.45 p.m., on "Responses of Nervous Tissue to Injury and Disease; Recent Advances in Knowledge."

Radio.—"The New Plagues," a talk by Professor E. M. BACKETT, professor of social medicine at Aberdeen, in "Science Survey," May 9, 6.30 p.m. on Network Three.

Croonian Lectures.—Dr. PAUL WOOD will lecture at the Royal College of Physicians on May 13 and 15, at 5 p.m., on "The Eisenmenger Syndrome, or Pulmonary Hypertension with Reversed Central Shunt."

Association of Medical Records Officers.—Conference, exhibition, and annual meeting at Harrogate, May 14–17. Details from Mr. A. E. J. TURNER, United Bristol Hospitals, Royal Infirmary Branch, Bristol, 2.

Louis Rapkine Memorial Lecture.—Dr. JACQUES MONOD, of the Pasteur Institute, Paris, will deliver the first Louis Rapkine memorial lecture on June 2 at the French Institute, Queensbury Place, London, S.W.7. His subject will be "The Permeases: Specific Factors of Cellular Permeability." Tickets may be obtained from the Institute of Biology, 41, Queen's Gate, London, S.W.7.

NEW ISSUES

British Journal of Ophthalmology.—Issued monthly (£6 annually). The new issue, Vol. 17, No. 1, includes:

VISUAL FIELD CHANGES PRODUCED BY *X*-RAY TREATMENT OF PITUITARY TUMOURS. Max Chamlin.
PSEUDO-TUMOUR OF THE ORBIT. Harvey Jackson.
EPIDERMOID AND DERMOID TUMOURS OF THE ORBIT. Patrick C. Carey.
TRAUMATIC CATARACT. P. Avasthy and R. B. L. Gupta.
BLASKOVICZ OPERATION. N. S. Jain.
A SIMPLE DIATHERMY MACHINE. J. Gibson Moore.
REMOVAL OF CORNEO-SCLERAL SUTURES. Peter Wilson.
A NEW TECHNIQUE IN CAMPIMETRY. J. V. Smith.

Medical and Biological Illustration.—Issued quarterly (£3 annually). The new issue, Vol. 8, No. 2, includes:

OCCUPATIONAL MARKS. F. Ronchese.
PRESERVATION AND CARE OF MATERIALS USED IN THE GRAPHIC ARTS IN THE TROPICS. Doig D. Simmonds.
NEW DEVELOPMENTS IN HALF-TONE BLOCKMAKING. F. W. Mackenzie.
THE BRUBAKER SPECULUM AND CAVITY SURGICAL FIELD MOTION PICTURE CAMERA. Joseph D. Brubaker.
PRESENT-DAY MATERIALS FOR INFRA-RED PHOTOGRAPHY. C. E. Engel.
SKULL-BONES—A STUDENT-PROOF TECHNIQUE. David Brown.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, May 5

LONDON UNIVERSITY.—At King's College, 5.30 p.m., special university lecture by Professor R. Huisgen (Munich): Recent Contributions to the Organic Chemistry of Nitrogen.
UNIVERSITY COLLEGE LONDON: DEPARTMENT OF BIOCHEMISTRY.—At Physiology Theatre, Gower Street, W.C., 5 p.m., public lecture by Dr. B. A. Stone: Biochemistry of Cellulose and Related Polysaccharides.
WRIGHT-FLEMING INSTITUTE OF MICROBIOLOGY.—5 p.m., Almroth Wright Lecture by Dr. Deborah Doniach: Thyroid Auto-immunity and its Clinical Implications.

Tuesday, May 6

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. G. B. Dowling: Scleroderma and Dermatomyositis.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. F. Avery Jones: Ulcerative Colitis.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Moynihan Lecture by Professor H. Rocke Robertson (British Columbia): Observations on Wound Infection.

Wednesday, May 7

ASSURANCE MEDICAL SOCIETY.—At Medical Society of London, 5 p.m., Dr. D. D. Reid: Occupation and Residence in Relation to Expectation of Life.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. W. Riddell: Histological Diagnosis of Fungus Infections.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. W. D. W. Brooks: Some Manifestations of Carcinoma of the Bronchus.
MANCHESTER MEDICAL SOCIETY.—At Physiology Theatre, Manchester University, 3.45 for 4.15 p.m., annual meeting. Sir Eric James: Education of the Scientist.
OXFORD UNIVERSITY.—At Radcliffe Infirmary, 5 p.m., Litchfield Lecture by Professor William Doolin: Abraham Colles and his Contemporaries.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. M. Bodian: Paediatric-Neoplastic Disease.
ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE: EDINBURGH BRANCH.—At West Medical Theatre, Royal Infirmary, Edinburgh, 5 p.m., symposium on Sleeping Sickness. Dr. A. D. Ross: Control of Sleeping Sickness in Nigeria; Dr. M. P. S. Hutchinson: Melarsen in the Treatment of Gambiense Trypanosomiasis; Dr. F. I. C. Apted: Mel. B. in the Treatment of Rhodesiense Trypanosomiasis.
UNIVERSITY COLLEGE OF SOUTH WALES AND MONMOUTHSHIRE.—At Reardon Smith Lecture Theatre, National Museum of Wales, Cardiff, 8 p.m., Second C. McLaren West Memorial Lecture by Sir Wilfrid le Gros Clark, F.R.S.: Anatomy of Prehistoric Man.

Thursday, May 8

COLLEGE OF GENERAL PRACTITIONERS: NORTH SCOTLAND FACULTY.—At Cumming's Hotel, Church Street, Inverness, 4.30 p.m., Pfizer Lecture by Dr. A. F. Anderson: Cancer Detection by Exfoliative Cytology.
GLASGOW UNIVERSITY AND ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW.—At Royal Faculty of Physicians and Surgeons, 3 p.m., conference on obstetrics and gynaecology. Dr. J. Bruce Dewar, Mr. R. S. Barclay, and Dr. M. D. Black: Cardiac Disease in Pregnancy.
HONYMAN GILLESPIE LECTURE.—At Anatomy Theatre, University New Buildings, Edinburgh, 5 p.m., Mr. H. A. F. Dudley: Neuro-Endocrine Response to Injury.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Miss Phyllis Wade: Radiation (Cancer I).
KENT PAEDIATRIC AND CHILD HEALTH SOCIETY.—2.45 for 3 p.m., visit to Chailey Heritage Craft School and Hospital.
LIVERPOOL MEDICAL INSTITUTION.—8 p.m. Joint History of Medicine Lecture by Dr. E. N. Chamberlain: African Slave Trade.

Friday, May 9

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. I. Muende: clinical demonstration.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. J. G. Scadding: clinical demonstration.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—3.30 p.m., clinical discussion for general practitioners by Dr. D. A. Osborn: Blood Diseases in Ear, Nose, and Throat Conditions.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—10 a.m., Mr. G. K. McKee: Artificial Hip Joints.
ROYAL COLLEGE OF SURGEONS OF EDINBURGH.—3.45 p.m., Sir David Wilkie Lecture by Mr. J. G. Murray: Responses of Nervous Tissue to Injury and Disease; Recent Advances in Knowledge.
ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Institute Theatre, 5 p.m., Brains Trust Panel, Mr. Donald Fraser, Professor W. C. W. Nixon, Mr. A. B. Evans, and Mr. I. M. Jackson. Question Master, Mr. Aleck Bourne.

Saturday, May 10

MIDLAND THORACIC SOCIETY.—At Cheshire Joint Sanatorium, Market Drayton, 11 a.m., joint meeting with North Western Tuberculosis Society. Professor Wilfrid F. Gaisford and Dr. H. J. T. Ross: Intrathoracic Primary Tuberculosis in Children; Dr. D. L. Caldwell and Dr. G. R. W. N. Luntz: Pulmonary Tuberculosis and Diabetes Mellitus.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Richardson.—On April 16, 1958, at Greystones, Islip, Oxford, to Pamela (formerly Durrant), wife of Dr. J. Derek Richardson, a son—Robert Duncan.

Trigg.—On April 19, 1958, at Beckenham Maternity Hospital, Beckenham, Kent, to Sylvia J. Jordan, M.B., B.S., wife of Kenneth H. Trigg, M.B., B.S., D.Obst.R.C.O.G., a second daughter—Hilary Anne.

DEATHS

Davies.—On April 8, 1958, at Victoria Hospital, Deal, Kent, Daniel Alexander Davies, F.R.C.S., of The Knoll, Walmer, Kent.
Emery.—On April 9, 1958, at 80 Southampton Street, Reading, Berks, Frederick Harold Emery, L.R.C.P.&S.Ed., L.R.F.P.S.
Goldstein.—On April 6, 1958, John Leopold Goldstein, M.R.C.S., L.R.C.P., aged 85.
Grattan.—On April 14, 1958, at his home, 51, Uphill Road, Mill Hill, London, N.W., Donald Arthur Grattan, M.B., Ch.B., aged 59.
Lunn-Rockcliffe.—On March 17, 1958, at 6, Barnes Close, Winchester, Hants, William Ernest Craven Lunn-Rockcliffe, *M.C.*, M.B., B.S., Lieutenant-Colonel, R.A.M.C. (retired).
Moody.—On April 7, 1958, at the home of his daughter, Chicago, Illinois, U.S.A., Arthur Stanley Moody, M.D., of Dunedin, New Zealand, aged 68.
Norris.—On April 8, 1958, Hélène Norris, M.D., of London, W.
Perigal.—On April 3, 1958, at Worthing General Hospital, Arthur de St. Leu Frederick Perigal, M.D., of 27, Pembroke Avenue, West Worthing, Sussex, late of New Barnet and Hatfield, Herts, aged 83.
Smith.—On April 4, 1958, at Fernwood, Farningham, Kent, Sumner Hugh Smith, *M.C.*, M.R.C.S., L.R.C.P., aged 71.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Poliomyelitis Vaccination of Close Contacts

Q.—*Do the brothers and sisters of a child attacked by poliomyelitis need to be vaccinated against the disease, or does the disease, once in the house, affect all the family at the same time?*

A.—It would be easier to answer the second part of the question first. Poliomyelitis is spread from person to person by contact; wherever contact is close, the risk of infection will be increased. In this respect the family presents highly favourable conditions. Multiple cases of poliomyelitis in families was recognized as an epidemiological feature of the disease more than forty years ago.[1] Subsequent work[2–4] showed this to be even more frequent when abortive cases were taken into account, the incidence being higher in families with children aged 1–10 years. The first clinical case in a family is often regarded as the first case, but in poliomyelitis, where inapparent infection is common, the first may often be an asymptomatic carrier. Recent epidemiological studies by Horstmann[5] and Paffenbarger *et al.*[6] indicate that members of the family in which a case of poliomyelitis occurs become faecal carriers of virus about the same time irrespective of whether they contract an asymptomatic, abortive, non-paralytic, or paralytic infection. Two further reports[7 8] on family infections are of particular interest in demonstrating the simultaneous onset of infection. This is confirmed by recent studies based on the detection of viraemia and specific antibody response (antibody conversion) which pin-points the time of onset more accurately. In one series reported by Bodian and Paffenbarger[9] all the 61 child household contacts of paralysed cases became infected as determined by antibody conversion, but in a smaller series of 23 contacts at least six children still had no antibody to any of the three types of poliomyelitis virus one month later. Although the chances of infection are clearly great it cannot be assumed that all members of a household will in all instances develop natural infection followed by immunity. It is therefore advisable to immunize brothers and sisters of a child attacked by poliomyelitis. If they are already immune further immunization will do no harm.

REFERENCES

1 Lavinder, C. H., Freeman, A. W., and Frost, W. H., *Publ. Hlth Bull. (Wash.)*, 1918, No. 91, 1.
2 Paul, J. R., Salinger, R., and Trask, J. D., *J. Amer. med. Ass.*, 1932, **98**, 2262.
3 Trask, J. D., Vignec, A. J., and Paul, J. R., ibid., 1938, **111**, 6.
4 Casey, A. E., Fishbein, W. I., and Bundesen, H. N., ibid., 1945, **129**, 1141.
5 Horstmann, D. M., *Bull. N.Y. Acad. Med.*, 1953, **29**, 910.
6 Paffenbarger, R. S., jun., Wilson, V. O., Bodian, D., and Watt, J., *Amer. J. Hyg.*, 1954, **60**, 63.
7 Zintek, A. R., ibid., 1947, **46**, 248.
8 Wenner, H. A., and Tanner, W. A., *Amer. J. med. Sci.*, 1948, **216**, 258.
9 Bodian, D., and Paffenbarger, R. S., jun., *Amer. J. Hyg.*, 1954, **60**, 83.

Direct Blood Transfusion

Q.—*Are direct whole-blood transfusions more reliable in treating shock and arresting haemorrhage than citrated blood transfusions?*

A.—Assuming that the "shock" is produced mainly by haemorrhage, it may be said with some certainty that shock can be just as satisfactorily relieved by a transfusion of citrated blood as by the direct transfusion of whole blood. One considerable disadvantage of trying to treat a large haemorrhage by direct transfusion is the difficulty of securing at short notice an adequate number of donors. Moreover, the technique of direct transfusion is certainly more difficult than the technique of indirect transfusion—that is to say, using citrated blood. In addition, there can be few doctors now practising who would know how to carry out a direct transfusion. Direct transfusion probably supplies more viable platelets to the recipient than does the transfusion of citrated blood, particularly when the blood has been drawn into ordinary glass bottles, but this fact would not be of any importance unless very large amounts of blood (2–3 litres) were being transfused. Platelet deficiency is commonly found in patients who have lost very large amounts of blood and received massive transfusions, but it has been found that even transfusions of blood freshly drawn into plastic equipment fail to raise the platelet level in such patients,[1] and presumably direct transfusion would be no more successful.

REFERENCE

1 Krevans, J. R., and Jackson, D. P., *J. Amer. med. Ass.*, 1955, **159**, 171.

Serotherapy for Herpes Zoster

Q.—*Is serotherapy ever used in the treatment of herpes zoster and if so with what effect?*

A.—Serotherapy has been tried on numerous occasions in the treatment of zoster, as it has in many other virus infections, without effect. On theoretical grounds the use of serum is not likely to exert much effect in a disease like zoster when symptomatic illness has already started. Passive immunization with serum or gamma globulin is most effective when given close to the date of contact, which for practical purposes means during the incubation period in most instances. The use of serum as a prophylactic is more likely to be of value in varicella, but even here the results are equivocal.

Local Reaction to Triple Antigen

Q.—*A baby developed a local reaction, which quickly passed off, five hours after a triple-antigen injection. Should any precautions be taken when the next injection is given?*

A.—The triple antigen mentioned by the questioner is presumably the diphtheria-tetanus-pertussis prophylactic without alum. Some local redness and tenderness after the injection of the plain pertussis vaccine is occasionally seen in infants, especially if the injection has been given subcutaneously and not intramuscularly. They pass off as a rule within 36 hours. A second injection of the same triple antigen may safely be given (in the absence of poliomyelitis prevalence) after the usual interval of one month. If the first injection really disturbed the baby, the second dose could be halved and given intramuscularly.

Surgery and Epilepsy

Q.—*What place has surgery in the treatment of temporal lobe epilepsy?*

A.—The surgical treatment of temporal lobe epilepsy is at present in the experimental stage. Having determined electroencephalographically that the abnormality is confined to one temporal lobe, the anterior portion of this lobe is excised. It is claimed that half of the patients so treated are benefited—at the cost of a memory defect of varying severity and a homonymous field defect. The place of surgery in the treatment of the condition is by no means clearly defined. It should be employed only in carefully selected cases when adequate medicinal treatment has failed.

Pregnancy and Otosclerosis

Q.—*Is deafness from otosclerosis made worse by pregnancy?*

A.—The evidence for the common belief that deafness due to otosclerosis is made worse by pregnancy has recently been reviewed.[1] Of 243 patients investigated, 104 (43%) stated that their deafness had been made worse as a result of pregnancy. Audiometric examinations were carried out in 110. In only 19 had hearing deteriorated, and in 13 of these the hearing loss occurred three to five years after

pregnancy and might thus be attributed to the natural course of the disease. It was concluded that there is no evidence that pregnancy has a significant effect upon deafness due to otosclerosis. The risks of transmission to offspring, moreover, are slight, and to forbid child-bearing or induce abortion is not justified.

REFERENCE

1 Walsh, T. E., *J. Amer. med. Ass.*, 1954, **154**, 1407.

Resuscitation Equipment

Q.—*I am the medical member of an underwater swimming club, whose members dive in sea and fresh water with "aqualungs." What resuscitation equipment should I carry on diving expeditions?*

A.—By far the most useful piece of equipment would be Eve's rocking stretcher, and a plank over a rock will do for this in an emergency. This method not only gives a good tidal volume and helps lung drainage, but also, most importantly, supports the circulation (and may even create an artificial one). Any form of hand or mechanical bellows or cuirass is at this stage contraindicated, since they must impair circulation, already in many cases undetectable by normal clinical means. It is doubtful whether intubation would be worth the time taken to do it, since if there is no laryngeal spasm it is unnecessary, and if there is spasm the attempts would make it worse. A laryngoscope and foot sucker might, however, help in a quick toilet of the lower parts of the pharynx and larynx. Oxygen might be of value, but it is no substitute for artificial respiration of a depth sufficient to remove the accumulated carbon dioxide.

Diet in Corticotherapy

Q.—*Are there any dietary considerations, apart from sodium restriction and potassium supplementation, during corticotherapy?*

A.—Most patients receiving corticotherapy do not need dietary regulation of any kind. It is only when high dosages of corticotrophin or steroids are used that this becomes necessary. Apart from the usual indications for regulation of sodium and potassium intake a troublesome increase of appetite and gain in weight may become manifest. This may entail an appropriate reduction of caloric intake, depending of course on the activity of the patient, and is most important in those patients with hypertension and any tendency to cardiac decompensation. Dexamphetamine sulphate is a considerable aid in overcoming this appetite problem. The problem of preventing osteoporosis has not been adequately solved. The development of this condition appears to be a function of dosage, sensitivity, and the age of the patient. It may be impossible to find a dose which will control the patient's disease without producing osteoporosis. Clearly, the protein intake must be adequate, and if any reduction of calories is necessary it should be at the expense of the intake of fat and carbohydrates.

Addison's Disease and Marriage

Q.—*What are the prospects for a woman aged 24 with well-controlled Addison's disease and about to be married?*

A.—Well-controlled Addison's disease should not affect fertility to any significant extent, and control does not become more difficult when conception occurs. The same precautions should be adopted during delivery as would be used during a surgical operation—i.e., increased cortisone. There is little evidence of a hereditary tendency, though one or two instances have been recorded.[1] A number of cases of Addison's disease in siblings have also been reported,[2–4] but it seems fairly clear that these are uncommon occurrences. No deleterious effects on the foetus are to be expected if the disease in the mother is well controlled. Over-dosage with cortisone could lead to abortion.

REFERENCES

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2 Hewitt, P. H., *Brit. med. J.*, 1957, **2**, 1530.
3 Symonds, C. P., ibid., 1958, **1**, 100.
4 Gordon, R. R., ibid., 1958, **1**, 400.

Rectal Drug Absorption

Q.—*What drugs are absorbed from the rectum?*

A.—A large number of drugs are probably absorbed from the rectum, but there is little definite information on this. Bromethol is always given per rectum, and paraldehyde sometimes. Hydrocortisone has been given per rectum to treat ulcerative colitis.[1 2] Morphine, of course, can be given per rectum, and so can glucose. Peptone is not absorbed per rectum. Among chemical substances, those which contain quaternary nitrogen, such as hexamethonium, are poorly absorbed from the alimentary tract (including the rectum), while those which contain primary, secondary, or tertiary nitrogen are absorbed fairly well. This includes many alkaloids.

REFERENCES

1 Truelove, S. C., *Brit. med. J.*, 1956, **2**, 1267.
2 —— ibid., 1957, **1**, 1437.

NOTES AND COMMENTS

Benzidine a Carcinogen.—Dr. T. S. SCOTT (Manchester) writes: Your expert is wrong in stating that the manufacture of benzidine has been discontinued in Great Britain ("Any Questions?" March 29, p. 783). It is, in fact, made on a large scale in this country, and in all other countries where dyestuffs are synthesized. It is the manufacture of beta-naphthylamine, the most potent of the industrial bladder carcinogens,[1] which has been abandoned,[2] at least in all Western countries, because of the danger associated with it. While ortho-tolidine and other substitutes for benzidine can be used for the detection of occult blood in the faeces, there is no substitute for it in the manufacture of certain essential dyes. Fortunately, it is a less potent carcinogen than beta-naphthylamine. A code of working practice[3 4] has been recommended by the British dyestuffs industry which lays down safe methods of manufacturing and handling, and gives details of the medical supervision of workers. It is believed that these recommendations will reduce the incidence of bladder tumours in workers to a level no greater than that which prevails in the general population.

OUR EXPERT replies: I agree with Dr. Scott's observations. The discrepancy is due to the fact that I was referring to purified benzidine of the degree required for chemical work. At the time of writing this was not being produced in England. However, quite recently one group of fine chemical manufacturers is occasionally purifying benzidine for laboratory use in small batches using special precautions.

REFERENCES

1 Case, R. A. M., Hosker, M. E., McDonald, D. B., and Pearson, J. T., *Brit. J. industr. Med.*, 1954, **11**, 75.
2 Scott, T. S., ibid., 1952, **9**, 127.
3 —— and Williams, M. H. C., ibid., 1957, **14**, 150.
4 Crabbe, J. G. S., Cresdee, W. C., Scott, T. S., and Williams, M. H. C., ibid., 1956, **13**, 270.

Corrections.—In the paper on "Encephalitis and Influenza" by Drs. J. M. Dunbar, W. M. Jamieson, Jean H. M. Langlands, and G. H. Smith (April 19, p. 913), the last sentence of the first paragraph on p. 914 should have begun with the words "There was a rod-cell reaction . . ."

In the annotation on chlorothiazide last week (April 26, p. 990) we wrongly stated that 2 g of the drug costs 7s. 6d. The basic N.H.S. price is 1s. 10½d. for 2 g.

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